UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: February 12, 2003

SUBJECT: **Metolachlor**. Revised HED Science Assessment for the Tolerance Reassessment Eligibility Decision, Including the Pending Petitions on Asparagus, Carrot, Horseradish, All Peppers, Rhubarb, Sugar Beet, Sunflower, Swiss Chard, Tomato, Spinach, and Grasses Grown for Seed.

PC Code:	108801
Case No.:	289117
40 CFR 180.	368
DP Barcode:	D288263
Petition Nos.:	7F4897, 9E6055, 7E4916, 2E6374, 4E4420, 8E5029
Submission No.:	S609428

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and

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Attached is the **revised** tolerance reassessment eligibility decision document for metolachlor and s-metolachlor, prepared by the Health Effects Division (HED). This assessment has been revised to take into consideration the pending petitions for asparagus, carrot, horseradish, all peppers, rhubarb, sugar beet, sunflower, Swiss Chard, tomato, spinach, and grasses grown for seed. HED notes that no changes to the toxicological endpoint selection or the residue chemistry chapter have been made in this revised assessment, nor have any of the proposed new uses resulted in a significant change to the risk picture for metolachlor and s-metolachlor. New estimated dietary risks of metolachlor/s-metolachlor in food have **not** resulted in a significant change to the aggregate risk assessment.

This assessment includes the hazard characterization from Virginia Dobozy, residential exposure assessment from Richard Griffin, dietary exposure and residue chemistry assessments from Sherrie Kinard, product chemistry from Ken Dockter, drinking water assessment from Mark Corbin, and aggregate exposure assessment and risk characterization from Christina Jarvis and Sherrie Kinard. The disciplinary science chapters and other supporting documents referenced in this document are as follows:

- Revised Estimated Drinking Water Concentrations for Metolachlor/S-Metolachlor and its Degradation Products for Use in the Human Health Drinking Water Risk Assessment. M. Corbin, 05/22/02.
- Product Chemistry Chapter for the Tolerance Reassessment Eligibility Decision (TRED) Document. K. Dockter, 2/06/02. D274330.
- Response to "SCAN [only] of PMRA's Review of Product Chemistry. K. Dockter, 04/19/02. D281758.
- S-metolachlor. Supplemental Product Chemistry [Storage Stability; OPPTS Guideline No. 830.6317]. MRID 44183001 [Addendum to MRID 43928903]. K. Dockter, 05/22/02. D283040.
- Report of the Hazard Identification Assessment Review Committee. V. Dobozy, 9/28/01.
- Results of the HED Metabolism Assessment Review Committee Meeting Held on 8/14/01. V. Dobozy; 8/14/01. D274326.
- Report of the FQPA Safety Factor Committee. C. Christensen; 11/14/01.
- Revised Metolachlor and S-Metolachlor Residue Chemistry Chapter for the Tolerance Reassessment Eligibility Decision (TRED) Document. S. Kinard; 05/22/02. D282931.
- Revised Toxicology Chapter for Metolachlor/S-Metolachlor. V. Dobozy, 05/13/02. D282934.
- Metolachlor. Review of Six Acute Toxicity Studies. V. Dobozy, 05/21/02. D283039.
- **PP#'s: 7F4897, 9E6055, 7E4916, 2E6374, 4E4420, 8E5029: Metolachlor and *S*-Metolachlor**. Acute and Chronic Dietary Exposure Assessments for the Revised Tolerance Reassessment Eligibility Decision (TRED) and Proposed New Uses. S. Kinard; 02/12/03. D288263.
- Metolachlor/S-Metolachlor: Residential Risk Assessment. R. Griffin, 2/20/02. D274331.
- Review of Metolachlor Incident Reports. J. Blondell and M. Spann, 8/15/97. D238112.
- Replacement of Metolachlor Technical (Racemic Metolachlor) with Alpha-Metolachlor Technical; Review of Bridging Data. L. Kutney, 11/12/96. D226780.

TABLE OF CONTENTS

Background

Metolachlor is a chloroacetanilide herbicide that was first registered for use in 1976. Racemic metolachlor consists of 50% each of the R-enantiomer (CGA 77101) and the S-enantiomer (CGA 77102, or alpha metolachlor). The S-enantiomer is the herbicidally active isomer. In 1996, the registrant (originally Ciba-Geigy, now Syngenta) proposed a process to produce a higher ratio of CGA 77102:CGA 77101 (88:12 instead of 50:50) and applied for reduced-risk status based on similar efficacy at decreased application rates (the application rate of s-metolachlor is approximately 36 percent lower than that of metolachlor). In 1997, the EPA approved the registration of s-metolachlor as a reduced-risk product.

Syngenta no longer holds any active registrations for (racemic) metolachlor end-use products or (racemic) metolachlor technical product; however, until the residue chemistry chapter can be updated (currently underway), the Agency will proceed with a tolerance reassessment decision for racemic metolachlor, based on all crops granted by the technical label. The Agency notes, however, that since the use pattern of s-metolachlor is similar to that of racemic metolachlor, and since the Agency has determined that s-metolachlor has either comparable or decreased toxicity as compared to racemic metolachlor, this document is reflective of s-metolachlor as well.

1.0 Executive Summary

The Agency has conducted a revised human health risk assessment for the active ingredient metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] for the purpose of making a tolerance reassessment eligibility decision. Since the Reregistration Eligibility Decision (RED) document for metolachlor was completed prior to the passage of the Food Quality Protection Act (FQPA) of 1996, a tolerance reassessment eligibility decision, or TRED, is now required. This assessment only discusses the human health risk assessment required for reassessment of tolerances, and does not include an occupational risk assessment required for reregistration of products. As noted above, this TRED for metolachlor is also representative of the uses of s-metolachlor.

Usage Information

Metolachlor and s-metolachlor are selective, chloroacetanilide herbicides used primarily for grassy weed control in many agricultural food and feed crops; residential lawns; commercial turf (including golf courses, sports fields, recreation areas, and sod farms); ornamental plants, trees, and shrubs, and vines; hedge rows; and horticultural nurseries. Corn, sorghum, and soybean account for the majority of the use of both metolachlor and s-metolachlor, followed by cotton, sweet corn, peanut, potato, and other minor field and vegetable crops.

Application rates for metolachlor and s-metolachlor range from approximately one to four pounds active ingredient (a.i.) per acre. Application is typically made pre-emergence, one time per season.

Syngenta does not currently hold any active end-use product registrations for metolachlor. S-metolachlor is registered by Syngenta under the trade names of Dual MAGNUM®, Pennant MAGNUM®, Bicep MAGNUM®, Boundary®, and Medal®. S-metolachlor is formulated mainly as an emulsifiable concentrate. Other formulations include flowable concentrates, granular, and ready-to-use formulations. Application methods for agricultural uses includes ground application (the most common application method), aerial application, irrigation systems, and chemigation (center pivot only). A backpack sprayer, hose-end sprayer, or handgun application may be used by professional applicators for application to residential lawns or turf. Residential applications to lawns and turf are intended for use by **professional applicators only**. The only currently active lawn/turf label is an emulsifiable concentrate formulation for s-metolachlor (Pennant MAGNUM®, EPA Reg. No. 100-950).

Hazard Identification and FQPA Considerations

The toxicology database for metolachlor is complete for risk assessment purposes. Metolachlor is moderately acutely toxic (toxicity category III) by the oral, dermal, and inhalation routes of exposure. It is not irritating to the skin or eyes, but is a dermal sensitizer. *The Agency notes that recently reviewed acute toxicity studies from 1994 show metolachlor to be moderately acutely toxic (toxicity category III) by the oral and dermal routes of exposure, and less toxic (toxicity category IV) by the inhalation route of exposure. These 1994 studies also show metolachlor to be a mild eye irritant (toxicity category III) and a minimal skin irritant (toxicity category IV).* In the subchronic and chronic toxicity studies, decreased body weight and body weight gain were the most commonly observed effects. There was no evidence that metolachlor was a reproductive or developmental toxicant. No systemic toxicity was observed when metolachlor was administered dermally at doses up to 1000 mg/kg/day. There was no evidence of mutagenic or cytogenetic effects *in vivo* or *in vitro*. Metolachlor has been classified as a Group C, possible human carcinogen based on liver tumors in rats at the highest dose tested. A linear risk assessment is not required.

The toxicology database for s-metolachlor, when bridged with the metolachlor database, is complete for risk assessment purposes. Bridging toxicology data from metolachlor, including acute toxicity, subchronic toxicity in rat and dog, developmental toxicity in rat and rabbit, mutagenicity, and metabolism studies are available. S-metolachlor is moderately acutely toxic (toxicity category III) by the oral and dermal route and relatively non-toxic (toxicity category IV) by the inhalation route of exposure. It causes slight eye irritation, and is non-irritating dermally but is a dermal sensitizer. In the subchronic studies, body weight and body weight gain decreases were the most commonly observed effects. There was no evidence that s-metolachlor was a developmental toxicant. There was no evidence of mutagenic or cytogenetic effects *in vivo* or *in vitro* with s-metolachlor.

Tolerances are established for the combined residues (free and bound) of metolachlor and its metabolites, determined as the derivatives 2-[(2-ethyl-6-methylphenyl)amino]-1-propanol (CGA-37913) and 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone (CGA-49751), each expressed as the parent compound, in or on raw agricultural commodities (40 CFR §180.368). The Metabolism Assessment Review Committee (MARC) determined that the residues of concern for plant and animal commodities are metolachlor and its metabolites, determined as the derivatives CGA-37913

and CGA-49751. Metabolites of metolachlor are assumed to be toxicologically equivalent to parent metolachlor. The residues of concern for s-metolachlor are the same as those for metolachlor (L. Kutney memo, 11/12/96).

Based on the Hazard Identification Assessment Review Committee (HIARC) decision that metolachlor and s-metolachlor are of comparable toxicity, studies of either chemical were used interchangeably for toxicology endpoint selection. Toxicological endpoints selected for risk assessment purposes are based on clinical signs of toxicity and decreased body weight gain. No evidence of neurotoxicity or neuropathology was seen in any of the available studies. A developmental neurotoxicity study is not required for metolachlor. Dermal absorption is calculated to be 58%, based on a dermal absorption study in rats, and inhalation absorption is assumed to be 100%.

In the case of metolachlor/s-metolachlor, risk assessments were conducted for the specific exposure scenarios listed below. Short- and intermediate-term dermal risk assessments were not conducted as no systemic toxicity was seen at the limit dose of 1000 mg/kg/day. The reference dose (RfD) is equal to the No-Observed-Adverse-Effect-Level, or NOAEL, divided by the 100X uncertainty factor.

– acute dietary(general population):	NOAEL= 300 mg/kg/day	RfD=3.0 mg/kg/day
– chronic dietary:	NOAEL= 9.7 mg/kg/day	RfD = 0.1 mg/kg/day
– short-term incidental oral:	NOAEL= 50 mg/kg/day	Target MOE=100

A total uncertainty factor (UF) of 100X was applied to the risk assessment to account for interspecies extrapolation (10X) and intraspecies variability (10X). The FQPA Safety Factor Committee has concluded that the FQPA safety factor for the protection of infants and children may be reduced to 1X (i.e., removed) for the dietary and residential risk assessments.

Dietary Exposure

An upper-end Tier 1 screening level acute dietary risk assessment was conducted for combined exposure to residues of metolachlor and s-metolachlor found on various field and vegetable crops. The assessment used tolerance level residues values and assumed that 100% of labeled crops were treated with metolachlor/s-metolachlor. This assessment is considered to be unrefined. Further refinements are not needed at this time. Since it is not possible to distinguish between residues of metolachlor and s-metolachlor using currently available enforcement methods, and since the tolerances for metolachlor presently cover residues resulting from the use of s-metolachlor, acute dietary risk estimates are applicable to both metolachlor and s-metolachlor. Acute dietary risk estimates are not of concern (i.e., below 100% of the acute population adjusted dose, or aPAD) at the 95th exposure percentile, for any population subgroup.

An upper-end Tier 1 chronic dietary risk assessment was also conducted for combined exposures to metolachlor and s-metolachlor. Tolerance level residue values and 100% crop treated were assumed. This assessment is considered to be unrefined. Further refinements are not needed at this time. As with the acute dietary risk assessment, chronic dietary risk estimates are applicable to both metolachlor and s-metolachlor. Chronic dietary risk estimates are not of concern (i.e., below 100% of the chronic

population adjusted dose, or cPAD) for any population subgroup.

The Agency notes that the Tier 1 acute and chronic dietary assessments could be further refined using available percent crop treated information, field trial and monitoring data, and processing factors; however, the estimated acute and chronic dietary risks are not of concern for any population subgroup. Further refinements are not warranted at this time. A separate cancer dietary risk assessment was not conducted, as it was determined that the chronic dietary endpoint would be protective of any cancer dietary risks.

In conjunction with a March 22, 2002 Federal Register notice that cancelled the existing use of metolachlor on stone fruits and almonds, stone fruits have been removed from this revised risk assessment. Almonds will remain in the dietary assessment, as there is a crop group tolerance that exists for tree nuts, and almonds are part of the tree nut crop group.

The Agency has agreed to include asparagus, carrot, horseradish, all peppers, rhubarb, sugar beet, sunflower, Swiss Chard, tomato, spinach, and grasses grown for seed in the tolerance reassessment. The residue chemistry data for sunflower, sugar beet, tomato, spinach and grasses grown for seed have been reviewed and deemed acceptable; however, a decision on the registration for these commodities cannot be made until an occupational assessment has been conducted. Since this is a tolerance reassessment document and not a reregistration eligibility decision document, an occupational assessment will not be done as part of this document. Asparagus, carrot, Swiss chard, all peppers, horseradish, and rhubarb are pending tolerances that have been included in the dietary risk assessment. The residue chemistry data for these commodities are currently under review. A decision on permanent tolerances for these commodities cannot be made until the residue chemistry data are reviewed.

Residential Exposure

Syngenta has no remaining residential end-use product labels for racemic metolachlor. S-metolachlor may be applied as an emulsifiable concentrate to residential lawns or turf by a **professional applicator only**. Therefore, residential handlers are not expected to be exposed to residues of s-metolachlor. A residential handler risk assessment was not conducted.

There is a potential for residential post-application exposure to residues of s-metolachlor that may remain on lawns after treatment by professional applicators. However, no toxic effects are expected by no short- and intermediate-term dermal exposure and no short- and intermediate-term dermal endpoints were selected (there was no systemic toxicity seen at the limit dose of 1000 mg/kg/day). Inhalation exposure is expected to be minimal as labels specify that residents should not enter treated areas until after sprays have dried; therefore, the only residential post-application scenarios that were assessed were potential oral exposure to children from contact with treated lawn and soil (i.e., object-to-mouth, hand-to-mouth, and incidental soil ingestion scenarios). These exposure scenarios are considered short-term in duration (one to 30 days of exposure), based on label specifications of a six week interval before the re-application of s-metolachlor. The registrant has also indicated a label revision to limit application to one application per season.

Post-application oral risk estimates are based on a single application of s-metolachlor at the maximum label rate of 2.47 lb ai/acre (EPA Reg. No. 100-950). The exposure values of the three scenarios (object-to-mouth, hand-to-mouth, and incidental soil ingestion) were combined to establish the possible, if not likely, upper-end estimate of oral exposure to children from lawn (or similar) use. Combined oral MOE estimates are 1100 for s-metolachlor. Post-application oral exposure from s-metolachlor is not of concern. The Agency acknowledges that Syngenta has no remaining residential end-use product labels for racemic metolachlor; however, for informational purposes, the combined oral MOE estimates for metolachlor (based on EPA Reg. No. 100-691 and a maximum label application rate of 4 lb ai/acre) are 670 and not of concern.

Drinking Water Exposure

A drinking water assessment was conducted based on monitoring data from several sources, as well as on Tier 1 FIRST and SCI-GROW modeling results. This assessment is a worst-case scenario and demonstrates high end number. **It is important to note that the analytical methods used to obtain the monitoring data are not able to distinguish between metolachlor and s-metolachlor; therefore, the estimated environmental concentrations (EECs) presented in this risk assessment are representative of both racemic metolachlor and s-metolachlor**.

EECs for metolachlor and s-metolachlor were calculated for both the parent compound and the ethanesulfonic acid (ESA) and oxanilic acid (OA) degradates. Although it was determined by the Metabolism Assessment Review Committee that the ESA and OA metabolites appear to be less toxic than parent metolachlor, they are included in the risk assessment (ESA and OA are not part of the tolerance expression and are not included in the dietary assessment) since they were found in greater abundance than the parent in water monitoring studies.

Revised surface water EEC values for parent metolachlor/s-metolachlor range from 4.3 ppb (chronic) to 77.6 ppb (acute) in monitoring data. The ground water EEC value for parent metolachlor/s-metolachlor is 5.5 ppb, based on modeled estimates. The EEC values of the ESA and OA degradates range from 22.8 ppb to 91.4 ppb in surface water, and from 31.7 ppb to 65.8 ppb in ground water, based on modeled estimates. These values are all below the Agency's estimated drinking water levels of comparison (DWLOCs), and therefore aggregate exposure to metolachlor/s-metolachlor is not likely to exceed HED's level of concern for human health.

Aggregate Exposure

Aggregate risk assessments for metolachlor/s-metolachlor consider the combined risk from exposure to residues via the food, drinking water, and residential pathways of exposure. In the case of metolachlor/s-metolachlor, food, drinking water, and post-application oral exposure to children (post-application oral exposure values are from the use of s-metolachlor only) will be considered in the aggregate assessment. The acute aggregate risk estimate is based on combined exposure to food and drinking water only, and is below HED's level of concern. The short-term aggregate risk assessment is based on food, drinking water, and short-term post-application oral exposure to children (s-metolachlor only). Short-term aggregate risk estimates are below HED's level of concern. The chronic aggregate risk assessment is based on food and drinking water exposure only, as there are no

long-term post-application exposure scenarios. Chronic aggregate risk estimates are below HED's level of concern.

Occupational Exposure
Occupational exposures and risks are not considered under FQPA; therefore, an occupational risk assessment is not included in this FQPA tolerance reassessment document.

Data Needs
Toxicology data gaps for metolachlor and s-metolachlor include a 28-day inhalation study in rats. Submission of these studies would allow the Agency to improve characterization regarding the concern for toxicity via the inhalation route of exposure. Registrants are recommended to follow the protocol for the 90-day inhalation study provided in OPPTS Guideline 870.3465, but cease exposure at 28 days.

Numerous residue chemistry data gaps, as well as several product chemistry data gaps, have been identified for metolachlor and/or s-metolachlor. These are identified in Section 7.0 of this document.

2.0 Physical/Chemical Properties Characterization

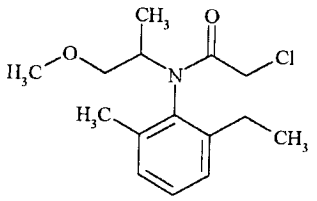
Metolachlor [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylphenyl)acetamide], a List A chemical, and its enriched isomer *s*-metolachlor are registered for selective weed control in many field and vegetable crops, ornamentals, lawns, and turf.

Metolachlor is a pale yellow to light brown liquid with a boiling point of 334°C; density of 1.117 g/cm^3 at 20°C; log P_{ow} of 3.05 at 25°C; and a low vapor pressure of 2.8×10^{-5} mm Hg at 25°C. Metolachlor is completely miscible in n-hexane, methanol, acetone, toluene, and n-octanol at 25°C.

No impurities of toxicological concern have been identified for metolachlor or s-metolachlor.

Product chemistry data requirements are essentially complete for both metolachlor and s-metolachlor. Any product chemistry data gaps that have been identified in the product chemistry chapter are listed in Section 7.0 of this document (K. Dockter memo, 2/06/02; revised by K. Dockter memo, 4/19/02).

Empirical formula:	$C_{15}H_{22}NO_2Cl$
Molecular weight:	283.8
CAS Registry Nos.:	51218-45-2 and 87392-12-9
PC Codes:	108801 & 108800

Common name/Chemical name	Chemical Structure
Metolachlor **2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl) acetamide**	

3.0 Hazard Characterization

3.1 Hazard Profile

Metolachlor:
The metolachlor toxicology database is complete for risk assessment purposes. Metolachlor is moderately acutely toxic (toxicity category III) by the oral, dermal, and inhalation routes of exposure. It is not irritating to the skin or eyes, but is a dermal sensitizer. *The Agency notes that the reviewed acute toxicity studies from 1994 show metolachlor to be moderately acutely toxic (toxicity category III) by the oral and dermal routes of exposure, and less toxic (toxicity category IV) by the inhalation route of exposure. These 1994 studies also show metolachlor to be a mild eye irritant (toxicity category III) and a minimal skin irritant (toxicity category IV).*

In the subchronic oral studies, the only evidence of toxicity was decreased body weight/body weight gain at 259 mg/kg/day in female rats and at 29 mg/kg/day in male and female dogs. The respective No Observed Adverse Effect Levels (NOAELs) for these studies were 23 mg/kg/day and 9 mg/kg/day. There was no evidence of systemic toxicity when 1000 mg/kg/day was applied topically to rabbits. Dermal irritation was observed at 10 mg/kg/day and above.

Similar effects were seen after long-term administration of metolachlor. In the chronic dog study, the only adverse effect was decreased body weight gain in females at 33 mg/kg/day; the NOAEL was 10 mg/kg/day. In the mouse carcinogenicity study, possible treatment-related deaths in females and decreased body weight/body weight gain in both sexes were observed at 450 mg/kg/day; the NOAEL was 150 mg/kg/day. In the rat combined chronic toxicity/carcinogenicity study, decreased body weight gain and food consumption were observed at 150 mg/kg/day; the NOAEL was 15 mg/kg/day. There was no evidence of carcinogenicity in mice; however, there were statistically significant increases in liver adenomas and combined adenomas/carcinomas in female rats. In male rats, there was a statistically significant trend but not pair-wise significance for liver tumors. There was no evidence of a mutagenic or cytogenetic effects *in vivo* or *in vitro*.

HED's Cancer Assessment Review Committee has classified metolachlor as a Group C carcinogen with risk quantitated using a non-linear approach. The NOAEL of 15 mg/kg/day from the rat combined chronic toxicity/carcinogenicity study is based on neoplastic nodules/hepatocellular carcinomas seen at the highest dose tested of 150 mg/kg/day. The Agency notes that the tumor NOAEL of 15 mg/kg/day

is comparable to the NOAEL of 9.7 mg/kg/day selected for establishing the chronic reference dose for metolachlor. The recommendation for a non-linear approach should be followed since no new data were submitted for a re-evaluation by the Cancer Assessment Review Committee.

The prenatal developmental studies in the rat and rabbit revealed no evidence of a qualitative or quantitative susceptibility in fetal animals. In the rabbit prenatal developmental toxicity study, at 360 mg/kg/day, maternal animals had persistent anorexia and decreased body weight gain; the NOAEL was 120 mg/kg/day. In the rat prenatal developmental toxicity study, frank toxicity [death, clinical signs (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive salivation) and decreased body weight gain] was observed at the limit dose of 1000 mg/kg/day in maternal animals; the NOAEL was 300 mg/kg/day. The developmental effects at 1000 mg/kg/day included slightly decreased number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight. In the two-generation reproduction study in rats, there was no evidence of parental or reproductive toxicity at approximately 80 mg/kg/day, the highest dose tested. At this dose, there was a minor decrease in fetal body weight beginning at lactation day 4; the NOAEL was approximately 25 mg/kg/day. Since a similar body weight decrease was not seen on lactation day zero, the cause of the effect on later lactation days is most likely due to exposure of the pups to metolachlor in the diet and/or milk and therefore is not evidence of an increased quantitative susceptibility in post-natal animals.

A series of acute, subchronic, developmental (rat) and mutagenicity studies were conducted on the ethane sulfonic acid (ESA, or CGA 354743) and oxanilic acid (OA, or CGA 51202) metabolites found in water. The MARC concluded that the ESA and OA metabolites appear to be less toxic than parent metolachlor/s-metolachlor, based on subchronic studies in the rat and dog (ESA metabolite only) and developmental studies in the rat. No toxicity was observed in any of these studies at the limit dose(s) of 1000 mg/kg/day or greater. Since a dose for toxicity of the metabolites was not demonstrated, the degree of difference between metabolite and parent could not be established. Acute toxicity was essentially comparable, except both metabolites were moderate (ESA) or severe (OA) eye irritants, whereas the parent compound was not. However, the MARC concluded that the ESA and OA metabolites should be included in the water risk assessment (not in the tolerance expression and not in the dietary assessment) since they were found in greater abundance than the parent(s) in water monitoring studies and assuming the toxicity of the degradates are equivalent to metolachlor. In addition, parent metolachlor has been classified as a Group C carcinogen. Without long-term studies in rats and mice with the metabolites, there are no data to substantiate that the metabolites are not carcinogenic.

One toxicology data gap exists for metolachlor, as there is concern for toxicity by the inhalation route following exposure on multiple days in a commercial setting. A 28-day inhalation study in rats with metolachlor should be conducted. Registrants are recommended to follow the protocol provided in OPPTS Guideline 870.3465 (90-day inhalation study) but cease exposure at 28 days.

The acute toxicity profile for metolachlor is presented in Table 1a. For comparison purposes, the acute toxicity profile for metolachlor, based on the reviewed 1994 acute toxicity studies, is presented in Table 1b.

Table 1a: Acute Toxicity Profile of Metolachlor (PC Code 108801)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
870.1100	Acute Oral- Rats	00015523	LD_{50} = 2780 mg/kg	III
870.1200	Acute Dermal- Rabbit	00015526	LD_{50} = > 10 mg/kg	III
870.1300	Acute Inhalation- Rats	00015535	LD_{50} = > 1.75 mg/L	III
870.2400	Primary Eye Irritation- Rabbits	00015528	non-irritating	IV
870.2500	Primary Skin Irritation- Rabbits	00015530	non-irritating	IV
870.2600	Dermal Sensitization- Guinea pigs	00015631	positive	
870.6200	Acute Neurotoxicity-NA			

NA–study not required

Table 1b: Acute Toxicity Profile of Metolachlor (PC Code 108801) Based on 1994 Studies

OPPTS Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
870.1100	Acute Oral - Rat	43492001	LD_{50} = 3302 mg/kg (males); 2000 mg/kg (females); 2877 mg/kg (combined sexes)	III
870.1200	Acute Dermal - Rabbit	43492002	LD_{50} = > 2000mg/kg	III
870.1300	Acute Inhalation - Rat	43492003	LC_{50} = > 4.33 mg/L	IV
870.2400	Primary Eye Irritation - Rabbit	43492004	mild irritant	III
870.2500	Primary Skin Irritation - Rabbit	43492005	minimal irritant	IV
870.2600	Dermal Sensitization - guinea pig	43492006	positive	

S-Metolachlor:

The toxicology database for s-metolachlor, when bridged with the metolachlor database, is complete for risk assessment purposes. Bridging toxicology data, including acute toxicity, subchronic toxicity in the rat and dog, developmental toxicity in the rat and rabbit, mutagenicity, and metabolism studies are available. S-metolachlor is moderately acutely toxic (Toxicity Category III) by the oral and dermal routes of exposure and relatively non-toxic (Toxicity Category IV) by the inhalation route of exposure.

S-metolachlor causes slight eye irritation and is non-irritating dermally, but is a dermal sensitizer.

In one subchronic toxicity study in rodents with s-metolachlor, no effects were observed in male and female rats at the high dose of approximately 225 mg/kg/day. In another subchronic toxicity study in rats, decreased body weight/body weight gain, reduced food consumption and food efficiency and increased kidney weights in males were observed at 150 mg/kg/day; the NOAEL was 15 mg/kg/day. In the subchronic dog study, no effects were observed in dogs at the high dose of approximately 70 mg/kg/day.

There was no evidence of increased quantitative or qualitative fetal susceptibility in the prenatal developmental studies in rats and rabbits. In the rat, maternal toxicity [increased clinical signs of toxicity (pushing head through bedding) and decreased body weights/body weight gains, food consumption and food efficiency] was observed at 500 mg/kg/day; the NOAEL was 50 mg/kg/day. There were no developmental effects at 1000 mg/kg/day, the highest dose tested. In the rabbit, clinical signs of toxicity (little/none/soft stool) were observed at 100 mg/kg/day; the NOAEL was 20 mg/kg/day. No developmental effects were observed at 500 mg/kg/day, the highest dose tested. There was no evidence of a mutagenic or cytogenic *in vitro* or *in vivo* studies with s-metolachlor.

S-metolachlor is extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. Tissue residues were highest in whole blood. Metabolism studies were inadequate for comparing the metabolic pathways of metolachlor and s-metolachlor. However, based on a comparison of the findings in the available studies with both chemicals, it appears that s-metolachlor is of comparable toxicity to the racemic mixture (metolachlor).

One toxicology data gap exists for s-metolachlor, as there is concern for toxicity by the inhalation route following exposure on multiple days in a commercial setting. A 28-day inhalation study in rats with s-metolachlor should be conducted. The registrant is recommended to follow the protocol provided in OPPTS Guideline 870.3465 (90-day inhalation study) but cease exposure at 28 days.

The acute toxicity profile for s-metolachlor is presented in Table 1c:

Table 1c: Acute Toxicity Profile of S-Metolachlor (PC Code 108800)

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
870.1100	Acute Oral- Rats	43928915	LD_{50} = 3267 mg/kg (♂); 2577 mg/kg/day (♀); 2672 mg/kg/day (combined)	III
870.1200	Acute Dermal- Rabbit	43928916	LD_{50} = > 2000 mg/kg	III
870.1300	Acute Inhalation- Rats	43928917	LD_{50} = > 2.91 mg/L	IV
870.2400	Primary Eye Irritation- Rabbits	43928918	slight to moderate conjunctival irritation that cleared in 48 hours	III
870.2500	Primary Skin Irritation- Rabbits	43928919	non-irritating	IV
870.2600	Dermal Sensitization- Guinea pigs	43928920	positive	
870.6200	Acute Neurotoxicity–NA			

NA–study not required

3.2 FQPA Considerations

The FQPA Safety Factor Committee met on November 5, 2001 to evaluate the hazard and exposure data for metolachlor and s-metolachlor, and recommended that the FQPA Safety Factor for the protection of infants and children be **reduced to 1x** (removed) for the following reasons (Memorandum: Report of the FQPA Safety Factor Committee, Carol Christensen, 11/14/01):

i. The toxicology database is complete for the FQPA assessment;

ii. There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to metolachlor in the available toxicity data;

iii. A developmental neurotoxicity study is not required for metolachlor;

iv. The dietary (food and drinking water) and non-dietary exposure (residential) assessments will not underestimate the potential exposures for infants and children from the use of metolachlor.

3.3 Dose Response Assessment

Background:
Metolachlor (CGA 24705) consists of 50% each of the R-enantiomer (CGA 77101) and the S-enantiomer (CGA 77102, also referred to as alpha metolachlor). CGA 77102 is the isomer that is responsible for the herbicidal activity of metolachlor. The registrant developed a process to produce a higher ratio of CGA 77102:CGA 77101 (88:12) and in 1996 applied for reduced risk status based on decreased application rates. To support the registration of s-metolachlor, bridging toxicology data were submitted, including the following studies: six acute toxicity, subchronic toxicity in rat and dog, developmental toxicity in rat and rabbit and three mutagenicity studies. The registrant made the argument that CGA 77102 was already tested as part of the racemate. Based on the additional studies with CGA 77102, the quantitative dose-effect relationship of the racemate and the S-enantiomer were very similar. The HED RfD Peer Review Committee met on April 10, 1997 to determine whether the limited toxicological data were adequate to demonstrate that both s-metolachlor and metolachlor have identical properties and if so, the applicability of the data base for metolachlor in the safety evaluation of s-metolachlor and whether a separate RfD was required. The Committee concluded that, without metabolism studies and side-by-side subchronic studies conducted in the same strain of rat using comparable dose levels of test materials, the identification of any qualitative or quantitative differences in the toxicological properties of CGA 77012 and metolachlor was not possible.

The data (metabolism and subchronic toxicity studies) requested by the 1997 RfD Committee were submitted and reviewed. On August 14, 2001, the HED's Metabolism Assessment Review Committee met to determine if there is comparable metabolism of metolachlor and s-metolachlor. The MARC concluded that there are some deficiencies in the metabolism databases for metolachlor and s-metolachlor that prohibit a definitive conclusion about the comparable metabolism of the two chemicals. First, the study (MRID 44491402) in which there were side-by-side metabolic assays was conducted with only a single oral dose (0.5 mg/kg). Therefore, there are no data on high dose or repeated low-dose metabolism under the same study conditions. Second, a metabolic pathway was proposed for metolachlor (MRID 43164201) but not s-metolachlor. Third, most of the metabolites of both metolachlor and s-metolachlor have not been identified.

The MARC concluded that, given the lack of certain data, such as proposed metabolic pathway for s-metolachlor and identification of metabolites for both chemicals, and uncertainties about findings in some studies, such as quantitative differences in metabolites, it was not possible to determine if the metabolism of the racemic mixture and s-metolachlor are comparable. However, the Committee questioned how much this information contributed to assessing the relative toxicity of metolachlor and s-metolachlor. Given inherent variabilities in the results of the available metabolism studies, it was concluded that additional metabolism studies might not add more understanding than the current information.

The MARC has determined that the residues of toxicological concern are the same for both metolachlor and s-metolachlor.

Rationale for Endpoint Selection:
HED's Hazard Identification Assessment Review Committee (HIARC) met on September 6, 2001 and reviewed the toxicology databases for metolachlor and s-metolachlor with regard to the acute and chronic reference doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential risk assessments. **The HIARC concluded that s-metolachlor and metolachlor have comparable toxicity profiles. Studies with both chemicals were used interchangeably for toxicology endpoint selection.**

A complete toxicology profile for both metolachlor and s-metolachlor can be found in Tables 1 and 2 of Appendix A. A summary of the doses and endpoints selected for human health risk assessment is presented in Table 2 of this document. A more thorough explanation of the rationale for endpoint selection is included below:

Acute Dietary Endpoint: The acute RfD of 3.0 mg/kg/day is based on a prenatal developmental toxicity study in rats with **metolachlor**, and is calculated as the NOAEL (300 mg/kg/day) divided by the total uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variability). The acute endpoint is based on an increased incidence of death, clinical signs of toxicity (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation) and decreased body weight gain seen at the LOAEL of 1000 mg/kg/day. It is noted that although increased incidence of death is one of the effects seen, it was seen at a dose (1000 mg/kg/day) approximately three times higher than the dose (300 mg/kg/day) that caused these deaths; therefore, the Agency is confident that adequate safety is provided to protect the public from dietary exposure to residues of metolachlor. Since the FQPA safety factor is reduced to 1X, the acute RfD is equal to the aPAD. The PAD is a modification of the acute or chronic RfD to accommodate the FQPA safety factor, and is calculated as the RfD divided by the FQPA safety factor.

Since clinical signs are observed after a single oral dose of metolachlor, the duration and route of administration are appropriate for the risk assessment. Salivation alone is seen at 300 mg/kg/day; however, as this effect is most likely due to gastric irritation and there is no other evidence of treatment-related toxicity, the finding is not considered toxicologically significant. Developmental effects observed are not attributable to a single exposure and therefore, a separate endpoint has not been identified for females 13-50.

Chronic Dietary Endpoint: The chronic RfD of 0.10 mg/kg/day is based on a chronic toxicity study in dogs with **metolachlor**, and is calculated as the NOAEL (9.7 mg/kg/day) divided by the 100X UF. The chronic endpoint is based on decreased body weight gain in females at the LOAEL of 33.0 mg/kg/day. Since the FQPA safety factor is reduced to 1X, the chronic RfD is equal to the chronic PAD. The study duration and route of administration are appropriate for this risk assessment.

Short-term Incidental Oral: The short-term incidental oral NOAEL of 50 mg/kg/day, from a prenatal developmental toxicity study in rats with **s-metolachlor**, is based on increased incidence of clinical signs, decreased body weight/body weight gain, food consumption and food efficiency seen at the LOAEL (500 mg/kg/day) in maternal animals. The endpoint is appropriate for the population of

concern (infants and children). The Committee noted that the NOAEL (20 mg/kg/day) for the prenatal developmental toxicity study in rabbits with s-metolachlor (MRID 43928924) was lower than the 50 mg/kg/day from the rat developmental study. However, the endpoint was based on clinical signs of toxicity (increase in little/none/soft stool observations) at 100 mg/kg/day. Although there was a dose-related increase in this sign, it is not evidence of frank toxicity and was judged not be appropriate for risk assessment. Therefore, the rabbit study with s-metolachlor was not selected for this exposure scenario.

Intermediate-term Incidental Oral: The intermediate-term incidental oral NOAEL of 8.8 mg/kg/day, from a subchronic toxicity study in dogs with **metolachlor**, is based on decreased body weight gain seen at the LOAEL of 29.4 mg/kg/day. The endpoint and study duration are appropriate for the population of concern (infants and children).

Dermal Absorption: A dermal absorption value of 58% has been selected, based on an available dermal absorption study in rats with **metolachlor**. The percentage of the applied dose found in blood, urine, feces, carcass and cage was increased during the period between skin wash (10 hours) and sacrifice (72 hours). During the same period, the levels in the skin decreased by a similar amount. This observation suggested that metolachlor retained in skin was absorbed during the pre-sacrifice period. Therefore, the HIARC selected 58% dermal absorption value based on the combined values at 10 hours measurement (33%) and at the amount remaining on the skin (25%).

Short- and Intermediate-Term Dermal Endpoints: No hazard was identified for quantification of risk following dermal exposure. In a 21-day dermal toxicity study (MRID 41833101), no systemic toxicity was seen following repeated dermal application of metolachlor (96.4% a.i.) to the intact skin of five New Zealand rabbits/sex/group at doses of 0, 10, 100 or 1000 mg/kg/day for 21 days. No prenatal developmental toxicity studies with metolachlor or s-metolachlor were appropriate for this risk assessment. There was no evidence of developmental effects in rats or rabbits at maternally toxic doses with either metolachlor or s-metolachlor, except in the rat prenatal developmental toxicity study. In this study, there were slightly decreased number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight but only at 1000 mg/kg/day which was extremely toxic to dams (death, clinical signs of toxicity and decreased body weight gain).

Long-term Dermal Endpoint: The long-term dermal NOAEL of 9.7 mg/kg/day, from a chronic oral toxicity study in dogs with **metolachlor**, is based on decreased body weight gain in females at the LOAEL of 33.0 mg/kg/day. The treatment period (21-days) in the dermal toxicity study with metolachlor was not considered to be of sufficient duration for these compounds since effects seen in chronic oral studies could also be observed with long-term dermal administration. Therefore, the HIARC selected an oral NOAEL for this exposure scenario, and since an oral study was selected, the dermal absorption factor (58%) should be applied.

Short-term Inhalation Endpoint: The short-term inhalation NOAEL of 50 mg/kg/day, from an oral prenatal developmental toxicity study in rodents with **s-metolachlor**, is based on increased incidence of clinical signs, decreased body weight/body weight gain, food consumption and food efficiency at the LOAEL of 500 mg/kg/day in maternal animals. Since an oral study was selected, a 100% absorption factor should be applied.

Intermediate-Term Inhalation Endpoint: The intermediate-term inhalation NOAEL of 8.8 mg/kg/day, from a subchronic oral toxicity study in dogs with **metolachlor**, is based on decreased body weight gain at the LOAEL of 29.4 mg/kg/day. Since an oral study was selected, a 100% absorption factor should be applied.

Long-Term Inhalation Endpoint: The long-term inhalation NOAEL of 9.7 mg/kg/day, from a chronic toxicity study in dogs with **metolachlor**, is based on decreased body weight gain in females at the LOAEL of 33 mg/kg/day. Since an oral study was selected, a 100% absorption factor should be applied.

Target MOE for residential and aggregate exposure: A target MOE (NOAEL/exposure) is the level above which the Agency does not have a risk concern. For metolachlor, a target MOE of 100 is considered adequate for dermal and inhalation residential exposure, as well as for aggregate exposure. The target MOE of 100 includes the FQPA safety factor of 1X.

Table 2. Summary of Toxicological Dose and Endpoints for Metolachlor for Use in Human Risk Assessment

Exposure Scenario	Dose (mg/kg/day) and Uncertainty Factor (UF)	Endpoint for Risk Assessment	Study
Acute Dietary (all population subgroups)	NOAEL = 300 UF = 100x FQPA Safety Factor = 1x	death, clinical signs of toxicity (clonic and/or tonic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive salivation) and decreased body weight gain	Prenatal developmental toxicity study in rats with **metolachlor**
	Acute PAD = 3.0 mg/kg/day		
Chronic Dietary (all population subgroups)	NOAEL= 9.7 UF = 100 FQPA Safety Factor = 1x	decreased body weight gain in females	Chronic study in dogs with **metolachlor**
	Chronic PAD = 0.1 mg/kg/day		
Incidental Oral, Short-Term (one to 30 days)	NOAEL = 50 Target MOE = 100	increased incidence of clinical signs, decreased body weight/body weight gain, food consumption, and food efficiency	Prenatal developmental toxicity study in rats with **s-metolachlor**
Incidental Oral, Intermediate-Term (one month to 180 days)	NOAEL = 8.8 Target MOE = 100	decreased body weight gain	Subchronic (6 month) toxicity study in dogs with **metolachlor**
Dermal, Short- and Intermediate-Term	Hazard was not identified for quantification of risk. No systemic toxicity was seen at the limit dose (1000 mg/kg/day) following dermal applications and there is no concern for developmental toxicity in rats or rabbits.		
Dermal, Long-Term[a] (greater than 180 days)	Oral NOAEL = 9.7 Target MOE = 100	decreased body weight gain in females	chronic toxicity study in dogs with **metolachlor**
Inhalation, Short-Term[b]	Oral NOAEL = 50 Target MOE = 100	increased incidence of clinical signs, decreased body weight/body weight gain, food consumption, and food efficiency	Prenatal development toxicity study in rats with **s-metolachlor**
Inhalation, Intermediate-Term[b]	Oral NOAEL = 8.8 Target MOE = 100	decreased body weight gain	subchronic (6 month) toxicity study in dogs with **metolachlor**
Inhalation, Long-Term[b]	Oral NOAEL = 9.7 Target MOE = 100	decreased body weight gain in females	chronic toxicity study in dogs with **metolachlor**

* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.

19

[a] Since an oral NOAEL was selected, a dermal absorption factor of 58% should be used in route-to-route extrapolation.

[b] Since an oral NOAEL was selected, an inhalation factor of 100% should be used in route-to-route extrapolation.

3.4 Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, metolachlor may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Exposure Assessment and Characterization

4.1 Summary of Registered Uses

Metolachlor and s-metolachlor are broad-spectrum herbicides that are members of the chloroacetanilide group of pesticides. They are used primarily for grassy weed control in many agricultural food and feed crops (major crop uses include corn, soybeans, and sorghum); residential lawns (by certified applicator only); commercial turf (including golf courses, sports fields, recreation areas, and sod farms); ornamental plants, trees, and shrubs, and vines; hedge rows; and horticultural nurseries. Types of weeds controlled by metolachlor and s-metolachlor include, but are not limited to, the following: pigweed, carpetweed, waterhemp, chickweed, goosefoot, ragweed, broomweed, morning glory, crabgrass, witchgrass, foxtail, and nightshade.

[**NOTE**: *That Agency acknowledges that Syngenta no longer holds any active registrations for (racemic) metolachlor end-use products or (racemic) metolachlor technical products; however, until the residue chemistry chapter can be updated (currently underway) with the new registrations for (racemic) metolachlor held by Sipcam Agro USA, Inc.; Drexel Chemical Company; and TRI Chemical, Inc. (formerly Cedar Chemical), the Agency will proceed with a tolerance reassessment decision for racemic metolachlor, based on all crops that metolachlor may be used on, as allowed for by the technical label].*

Metolachlor and s-metolachlor are formulated as emulsifiable concentrates (most common), flowable concentrate, soluble concentrates, ready-to-use formulations, and as granular formulations. Application methods may include the following: ground application (most common), aerial application, irrigation systems, and chemigation (center pivot only). For residential lawns, a hose-end sprayer, **20**

backpack sprayer, or handgun application may be used. Application timing is as follows: pre-plant, at plant, pre-emergence, and postemergence. Metolachlor and s-metolachlor are generally applied one time per year. Application rates range from approximately one to four pounds a.i. per acre, with the application rate of s-metolachlor being approximately 35 percent less than that used historically for metolachlor.

This risk assessment is a tolerance reassessment only; therefore, exposures to occupational handlers of metolachlor/s-metolachlor are not assessed in this document. Potential sources of non-occupational exposure to metolachlor/s-metolachlor include exposure from residues in food and drinking water, and post-application exposure of homeowners and infants/children to residues of s-metolachlor remaining on treated lawns or turf. Non-occupational exposure from spray-drift is also discussed in this tolerance reassessment eligibility decision document.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

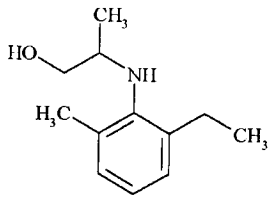
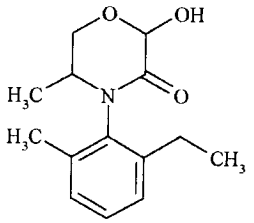
Tolerances for residues of both metolachlor and s-metolachlor in or on raw agricultural commodities include the combined residues (free and bound) of metolachlor and its metabolites, determined as the derivatives, CGA-37913 and CGA-47951, each expressed as parent compound. Permanent tolerances for metolachlor residues have been established on various plant commodities ranging from 0.1 ppm in/on numerous commodities to 30.0 ppm in/on peanut forage and hay [40 CFR §180.368(a)]. Time-limited tolerances associated with section 18 emergency exemptions have been established for metolachlor residues in/on grass forage and hay, spinach, and tomato commodities [40 CFR §180.368(b)]. Tolerances associated with regional registrations have also been established for metolachlor residues in/on dry bulb onions, cabbage, and various peppers (chili, Cubanelle, and tabasco) [40 CFR §180.368(c)].

Tolerances for metolachlor currently cover residues of s-metolachlor on the same commodities for the same use pattern when the maximum use rate of s-metolachlor is approximately 35 percent less than the historical use rate of metolachlor. Although s-metolachlor is applied at lower application rates than metolachlor, there are currently no data available to reassess the s-metolachlor tolerances at lower levels than metolachlor. However, HED does recommend that a separate tolerance section be established under §180.368 for s-metolachlor. Tolerances for metolachlor should be listed under §180.368(a)(1) through (d)(1), and tolerances for s-metolachlor should be listed under §180.368(a)(2) through (d)(2). A summary of the tolerance reassessment and recommended modifications in commodity definitions for metolachlor and s-metolachlor are presented in Appendix A, Tables 3 and 4, respectively.

Nature of the Residue in Plants:

The qualitative nature of metolachlor residues in plants is adequately understood based upon adequate corn, potato, and soybean metabolism studies. The metabolism of metolachlor involves conjugation with glutathione, breakage of this bond to form mercaptan, conjugation of the mercaptan with glucuronic acid, hydrolysis of the methyl ether, and conjugation of the resultant alcohol with a neutral sugar. A minor pathway may involve sugar conjugation of metolachlor directly to the corresponding oxo-compounds. Residues of concern in plants include metolachlor and its metabolites, determined as the derivatives CGA-37913 and CGA-49751. The structures of the metabolites are shown in Figure 1 below. The residues of concern for s-metolachlor are the same as for metolachlor (L. Kutney memo, D226780, 11/12/96); however, the Agency is currently reviewing additional submitted data (D278742 and D279110). These data will be incorporated into future assessments for metolachlor and s-metolachlor.

Figure 1. Chemical names and structures of metolachlor residues of concern in plants and animals.

Common names/(Codes) Chemical name	Chemical Structure
Metolachlor CGA-37913 2-[(2-ethyl-6-methylphenyl) amino]-1-propanol	
CGA-49751 4-(2-ethyl-6-methylphenyl)-2-hydroxy-5-methyl-3-morpholinone	

Nature of the Residue in Livestock:
Adequate studies are available depicting the metabolism of metolachlor in ruminants and poultry. Metolachlor is rapidly metabolized and almost totally eliminated in the urine and feces of ruminants (goats), non-ruminants (rats), and poultry. Metolachlor *per se* was not detected in any of the excreta or tissues. As in plants, metolachlor residues of concern in livestock commodities include metolachlor and its metabolites, determined as the derivatives CGA-37913 and CGA-49751. The residues of concern for s-metolachlor in animals are the same as for metolachlor; however, the Agency is currently reviewing additional submitted data (D278742 and D279110). These data will be incorporated into future assessments for metolachlor and s-metolachlor.

Residue Analytical Methods:
The Pesticide Analytical Manual (PAM) Vol. II, lists a GC/NPD method (Method I) for determining residues in/on plants and a GC/MSD method (Method II) for determining residues in livestock commodities. These methods determine residues of metolachlor and its metabolites as either CGA-37913 or CGA-49751 following acid hydrolysis. Residue data from the most recent field trials and processing studies were obtained using an adequate GC/NPD method (AG-612), which is a modification of Method I.

Multi-residue Method Testing:
Adequate data are available on the recovery of metolachlor through Multi-residue Method Testing Protocols. The FDA PESTDATA database indicates that metolachlor is completely recovered through Method 302, PAM Vol. I (3rd ed., revised 10/97).

Storage Stability Data:
Adequate storage stability data are available to support the crop field trials and processing studies. In plant commodities, the parent compound and all residues convertible to CGA-37913 are stable at ≤-10°C for at least 2 years in corn (grain and forage), peanut, potato (tubers, wet peel and flakes), soybean (hulls and meal), and tomato, for at least 29 months in cottonseed oil, and for at least 37 months in cottonseed and corn oil. The derivative CGA-49751 is also stable at ≤-10°C for at least 2 years in corn (grain, forage, and oil), peanut, potato (tubers, wet peel and flakes), soybean (hulls and meal) and tomato, and for at least 37 months in cottonseed and cottonseed oil.

For livestock commodities, data are available indicating that CGA-49751 is stable at -15°C for up to 25 months in milk, egg, beef liver and muscle. The derivative CGA-37913 is stable at -15°C for up to 25 months in milk and egg, 12 months in beef liver, and 2 months in beef muscle. More recent storage stability data for CGA-37913 indicated that it is stable at -20°C in beef muscle for up to 12 months; however, HED has concluded that the original storage stability studies for beef muscle were more representative of the conditions encountered during the feeding study; therefore, the original studies would be assumed to be valid and residues of CGA-37913 in beef muscle will be corrected for loss during frozen storage.

Magnitude of the Residue in Crops:

Adequate metolachlor residue data are available for both metolachlor and s-metolachlor to support tolerances in/on celery, corn (field and sweet), cottonseed, grasses grown for seed, potato, safflower, sorghum, sugar beet and sunflower. An adequate number of field trials have been conducted on these crops and depict residues resulting from the application of metolachlor at the maximum labeled or proposed use rate. Adequate metolachlor and s-metolachlor data are also available for legume vegetable foliage, peanuts, soybean, spinach, and tree nuts provided the specified metolachlor and s-metolachlor label amendments are made. There are adequate metolachlor data available for tomato; however, copies of the labels must be provided specifying a PHI of 90 days and a maximum of one post-emergence application of 3.0 lb ai/A for metolachlor, and 1.9 lb ai/A for s-metolachlor. The available residue data for metolachlor are summarized on a crop-by-crop basis in the residue chemistry chapter (S. Kinard memo, D282931, 5/22/2002, currently being updated to include new use information).

To support current or proposed tolerances for metolachlor and s-metolachlor, residue data are required reflecting the maximum use rates on the following crops or commodities: (i) representative succulent, shelled peas and beans, to support the use on legume vegetables; and (ii) bell peppers, to support a pending tolerance on peppers.

Maximum use rates for s-metolachlor are ~35 percent less than the use rate for metolachlor on comparable crops (see Appendix A, Table 3). The available bridging studies on corn and soybeans indicate that residues resulting from the application of s-metolachlor are likely to be lower than for metolachlor; therefore, the available metolachlor residue data will support comparable uses of s-metolachlor provided that the labeled use rates for s-metolachlor are ~35 percent lower than the metolachlor use rates. However, for those uses that result in residues well above the method LOQ (0.08 ppm), such as corn forage, residue data for s-metolachlor will be required to reassess tolerances if s-metolachlor completely replaces a particular use of metolachlor. Current examples of this include the special local need (SLN) uses on cabbage and dry bulb onions. Tolerances for both cabbage and dry bulb onion are 1.0 ppm, and all metolachlor SLN labels for these uses have been replaced by SLNs associated with s-metolachlor. Accordingly, residue data are required for s-metolachlor on cabbage and onions. For cases in which the current tolerance for metolachlor is set at or near the method LOQ, such as celery (0.1 ppm), additional s-metolachlor residue data will not be required if the comparable use of metolachlor is canceled.

Syngenta is proposing tolerances of 15.0 ppm in/on sugar beet tops, 0.5 ppm in/on sugar beet roots, and 0.5 ppm in/on sunflower seed for the combined residues of CGA-37913 and CGA-49751, each expressed as the parent compound. There were no residue chemistry deficiencies associated with the submitted data that would impact the eligibility of the active ingredient for registration.

Magnitude of the Residue in Processed Food/Feed:
Adequate processing studies are available for corn, cottonseed, peanut, potato, safflower, soybean sugar beet, sunflower and tomato; however, data depicting residues in corn, sorghum, and soybean aspirated grain fractions are required. The data from the corn, cottonseed and safflower studies indicate that metolachlor residues do not concentrate in processed commodities from these crops; however, the peanut, potato, soybean, and tomato processing studies indicated that there is the potential for concentration of metolachlor residues in several commodities. These data can be translated to support the use of s-metolachlor. A summary of the residue data by crop may be found in the residue chemistry chapter (S. Kinard memo, D282931, 5/22/2002, currently being updated to include new use information).

Syngenta is proposing tolerances of 1.0 ppm in sunflower seed meal, 1.0 ppm in sugar beet dried pulp and 3.0 ppm in sugar beet molasses for the combined residues of CGA-37913 and CGA-49751, each expressed as the parent compound; however, the proposed tolerances for molasses (3.0 ppm) are too high. The available data would support tolerances of 2.0 ppm in sugar beet molasses. A tolerance in sugar beet dried pulp will not be required because the concentration factor was only 1.1x, and the maximum expected residues in dried pulp (0.36 ppm) will not exceed the proposed tolerance for sugar beet roots (0.5 ppm). There were no residue chemistry deficiencies associated with the submitted data that would impact the eligibility of the active ingredient for registration; however, a revised section F proposing 2.0 ppm in/on sugar beet molasses and removal of the dried pulp tolerance must be submitted (see Appendix A, Table 3).

Magnitude of the Residue in Meat, Milk, Poultry, and Egg:
Tolerance reassessment requirements for magnitude of the residue in meat, milk, poultry, and egg are fulfilled. Adequate ruminant and poultry feeding studies are available for metolachlor, and these data will also support the use of s-metolachlor.

Confined Accumulation in Rotational Crops:
HED has concluded that the confined rotational crop study for metolachlor was inadequate but potentially upgradable. Additional data are required characterizing the ^{14}C-residues in plants, along with information on the percentage of the ^{14}C-residues measured by the current enforcement method, supporting storage stability data, and sample storage conditions and intervals. The Agency notes that additional confined accumulation data in lettuce, radish and wheat rotational crops have been submitted and are currently under review. These data will be included in future assessments.

Codex/International Harmonization:
No maximum residue limits (MRLs) for either metolachlor or s-metolachlor have been established or proposed by Codex, Canada, or Mexico for any agricultural commodity; therefore, no compatibility questions exist with respect to U.S. tolerances.

4.2.2 Dietary Exposure

Metolachlor and s-metolachlor acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM FCID™) software Version 1.3, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1994-1996, 1998. The 1994-98 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire US population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

For acute exposure assessments, individual one-day food consumption data are used on an individual-by-individual basis. The reported consumption amounts of each food item can be multiplied by a residue point estimate and summed to obtain a total daily pesticide exposure for a deterministic (Tier 1 or Tier 2) exposure assessment. The resulting distribution of exposures is expressed as a percentage of the aPAD on both a user (i.e., those who reported eating relevant commodities/food forms) and a per-capita (i.e., those who reported eating the relevant commodities as well as those who did not) basis. In accordance with HED policy, per capita exposure and risk are reported for all Tiers of analysis; however, for Tiers 1 and 2, significant differences in user vs. per capita exposure and risk are identified.

The DEEM FCID™ analyses estimated the acute and chronic dietary exposure for the general U.S. population and 26 population subgroups. The results reported in Table 3 are for the U.S. Population (total), all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and seniors 55 and older. The results for the other population subgroups are not reported in Table 3.

4.2.2.1 Acute Dietary Risk Estimates

A conservative Tier 1 acute dietary exposure assessment was conducted for all labeled metolachlor and all labeled and proposed s-metolachlor food uses. Inputs for this assessment included tolerance-level residue values and an assumption that 100% of all labeled crops were treated with metolachlor/s-metolachlor. For all supported, proposed, and registered commodities, the acute dietary exposure estimates are below the Agency's level of concern (<100% aPAD) at the 95th exposure percentile for the general U.S. population and all population subgroups (Table 3). The acute dietary risk estimate for the highest exposed population subgroup, children 1-2 years of age, is <1% of the aPAD.

4.2.2.2 Chronic Dietary Risk Estimates

A conservative Tier 1 chronic dietary exposure assessment was conducted for all supported metolachlor and s-metolachlor food uses. For all supported, proposed, and registered commodities, the chronic dietary exposure estimates are below the Agency's level of concern (<100% cPAD) for the general U.S. population and all population subgroups (Table 3). The chronic dietary risk estimate for the highest exposed population subgroup, children 1-2 years of age, is 4% of the cPAD.

The Agency notes that the conservative Tier 1 dietary assessments for metolachlor and s-metolachlor could be refined for more realistic dietary exposure estimates by using available percent crop treated estimates, field trial and monitoring data, and processing factors; however, further refinements are not warranted at this time.

Table 3. Summary of Dietary Exposure Estimates for Metolachlor and S-Metolachlor

Population Subgroup	Acute Dietary		Chronic Dietary		Cancer
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Risk
General U.S. Population	0.004111	<1	0.001643	2	NA
All Infants (< 1 year old)	0.006855	<1	0.002280	2	N/A
Children 1-2 years old	0.008224	<1	0.004025	4	
Children 3-5 years old	0.006965	<1	0.003510	4	
Children 6-12 years old	0.005003	<1	0.002412	2	
Youth 13-19 years old	0.003309	<1	0.001515	2	
Adults 20-49 years old	0.002815	<1	0.001263	1	
Females 13-49 years old	0.002965	<1	0.001349	1	
Adults 50+ years old	0.002839	<1	0.001226	1	

4.2.2.3 Cancer Dietary Exposure/Risk

Metolachlor has been classified as a Group C, possible human carcinogen, based on liver tumors in rats seen at the highest dose tested of 150 mg/kg/day. The Cancer Assessment Review Committee met on July 27, 1994, and determined that carcinogenic risks to metolachlor should be quantitated using a non-linear approach, with a NOAEL of 15 mg/kg/day based on neoplastic nodules/hepatocellular carcinomas seen at 150 mg/kg/day in the chronic toxicity/carcinogenicity study in rats. The Cancer Assessment Review Committee notes that the NOAEL used for calculating the cancer MOE values (15 mg/kg/day) is comparable to the NOAEL of 9.7 mg/kg/day selected for establishing the chronic reference dose for metolachlor. Therefore, a separate cancer dietary risk assessment was not conducted as it is assumed that the chronic PAD is protective for cancer dietary risk.

4.3 Water Exposure/Risk Pathway

A drinking water assessment for metolachlor and s-metolachlor was conducted by the Environmental 27

Fate and Effects Division (EFED) and involved the analysis of surface and ground water monitoring data, prospective ground water study data, and Tier I (FIRST and SCI-GROW) and Tier II (PRZM/EXAMS) modeling results. This assessment includes concentrations of parent metolachlor/s-metolachlor and the degradates metolachlor ethanesulfonic acid (ESA) and metolachlor oxanilic acid (OA). Although it was determined by the Metabolism Assessment Review Committee that the ESA and OA metabolites appear to be less toxic than parent metolachlor/s-metolachlor, they are included in this risk assessment since they were found in greater abundance than the parent in water monitoring studies.

The Agency notes that a key assumption of the drinking water assessment is that reported monitoring data represent both racemic metolachlor and s-metolachlor. The analytical methods for surface and ground water monitoring data used in this assessment are unable to distinguish between metolachlor and s-metolachlor. However, EFED believes that the fate properties of racemic metolachlor and s-metolachlor are similar. Therefore, **the EECs used in this risk assessment are representative of both racemic metolachlor and s-metolachlor**.

The environmental fate database is complete for metolachlor. Parent metolachlor/s-metolachlor appear to be moderately persistent to persistent, and range from mobile to highly mobile in different soils. Metolachlor/s-metolachlor have reportedly been detected as far as the 36 to 48 inch soil layer in some studies. Degradation appears to be dependent on microbially mediated and abiotic processes. The frequency of detection of metolachlor/s-metolachlor from evaluated monitoring data suggest that contamination in drinking water sources is widespread.

Environmental fate data comparing metolachlor and s-metolachlor indicate that both are expected to have similar degradation pathways and rates in soil and water environments, and both are expected to be mobile to highly mobile in soil and water environments.

EECs for Parent Metolachlor/s-Metolachlor:
No surface or ground water monitoring studies that specifically target metolachlor/s-metolachlor were available for the drinking water assessment. As a result, the drinking water assessment for parent metolachlor/s-metolachlor is based primarily on monitoring data from the following sources: the United States Geological Survey (USGS) National Water Quality Assessment (NAWQA) database, the US EPA STORET database, the Acetochlor Registration Partnership (ARP) database, and two USGS Reservoir Monitoring studies.

The acute estimated environmental concentration (EEC) of 77.6 ppb was selected from the NAWQA database, and the chronic EEC of 4.3 ppb was selected from the maximum annual time weighted mean from the NAWQA data. These values represent the estimated concentration of parent metolachlor/s-metolachlor in surface water, and are supported by the metolachlor concentrations from the National Contaminant Occurrence Database representing analysis of treated drinking water, as well as from model predictions using PRZM/EXAMS. When the monitoring data and modeling data are considered together, there is a general agreement between the various sources of information used in the assessment.

Acute and chronic concentrations of parent metolachlor/s-metolachlor in ground water were modeled using SCI-GROW. SCI-GROW estimates the upper bound ground water concentrations of pesticides likely to occur when the pesticide is used at the maximum allowable rate in areas with ground water **28**

vulnerable to contamination. Estimates were based on two applications to corn/turf for a total of 4 lbs ai/acre (the maximum application rate). In comparison to the SCI-GROW estimate of 5.5 ppb in shallow ground water, the Iowa NAWQA data have a maximum concentration of 15.4 ppb. However, it should be noted that the second highest concentration of parent metolachlor/s-metolachlor in the Iowa NAWQA data is 1.7 ppb. Additionally, recent data collected by the Suffolk Country, New York Department of Health Services, Bureau of Groundwater Resources indicate that both metolachlor and s-metolachlor, and its degradates, have been detected in ground water. In data collected between 1997 and 2001, metolachlor/s-metolachlor was detected in 60 well samples with a maximum concentration of 83 ppb. No information was available on frequency of detection and only summary statistics were provided on these data; therefore, these data were not used quantitatively in the risk assessment. However, these data suggest that the SCI-GROW estimates for metolachlor/s-metolachlor are not overestimating the potential impact of metolachlor/s-metolachlor use on ground water. Of note, parent metolachlor/s-metolachlor was not detected in two prospective ground water studies that have been completed. The SCI-GROW estimate of 5.5 ppb in ground water is appropriate for risk assessment purposes.

EECs for Metolachlor ESA and OA Degradates:

Only two small data sets were available on the ESA and OA degradates from the Iowa and Illinois NAWQA data. In the absence of more robust monitoring data for the degradates, upper-bound Tier I estimates for ESA and OA based on FIRST and SCI-GROW modeling were used to calculate EECs for the degradates. The modeling used conservative assumptions of selected fate parameters (aerobic soil metabolism rate constant and soil partitioning coefficient) as well as the maximum application rate of 4 lbs ai/acre on turf/corn.

Acute and chronic estimates of metolachlor ESA in surface water (based on FIRST modeling) are 31.9 ppb and 22.8 ppb, respectively. Acute and chronic estimates of metolachlor OA in surface water are 91.4 ppb and 65.1 ppb, respectively. The Agency notes that the application rate used for metolachlor ESA and OA in the model was estimated by converting maximum label rates for each use by the maximum percentage of degradate found in fate studies. In addition, each application rate was corrected for molecular weight differences of each degradate. However, EFED could not establish a statistically significant relationship between parent metolachlor and degradates; therefore, the amount of degradate is an uncertainty in this assessment.

Acute and chronic estimates of metolachlor ESA in ground water (based on SCI-GROW modeling, turf/corn scenario) are not expected to exceed 65.8 ppb. This value is considered representative of both peak and long-term average concentrations because of the inherent transport nature of ground water (generally slow movement from the source of contamination both laterally and horizontally). Acute and chronic estimates of metolachlor OA in ground water (also based on the turf /corn scenario) are not expected to exceed 31.7 ppb. The Agency notes that these values exceed those detected in the Iowa NAWQA study (63.7 ppb for metolachlor ESA and 4.4 ppb for metolachlor OA), and also exceed those values detected in two PGW studies (metolachlor ESA was detected at a maximum concentration of 24 ppb while metolachlor OA was detected at a maximum concentration of 15.6 ppb). In addition, recent data collected by the Suffolk Country, New York Department of Health Services, Bureau of Groundwater Resources indicate that both metolachlor and s-metolachlor, and its degradates, have been detected in ground water. In data collected between 1997 and 2001, metolachlor ESA was detected in 296 well samples with a maximum concentration of 39.7 ppb, while metolachlor OA was detected in 228 wells with a maximum concentration of 49.6 ppb. No informati

was available on frequency of detection and only summary statistics were provided on these data; therefore, these data were not used quantitatively in the risk assessment. However, these data suggest that the SCI-GROW estimates for metolachlor ESA and OA are slightly overestimating the potential impact of metolachlor/s-metolachlor use on ground water.

Drinking Water Levels of Comparison (DWLOCs):

In the absence of chemical-specific monitoring data, the Agency uses drinking water levels of comparison to calculate aggregate risk. A drinking water level of comparison, or a DWLOC, is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. In other words, the DWLOC value represents the maximum theoretical exposure a person may have to pesticide residues through drinking water, after their exposure to the pesticide's residues through food and residential exposure have been taken into consideration. The Office of Pesticide Programs uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. DWLOC values are not regulatory standards for drinking water; however, they do have an indirect regulatory impact through aggregate exposure and risk assessments.

DWLOCs are calculated for each type of risk assessment as appropriate (acute, short-term, intermediate-term, chronic, and cancer) and compared to the appropriate estimated concentration of a pesticide in surface and ground water, as provided by EFED. If the DWLOC is greater than the estimated surface and ground water concentration, (i.e., if the DWLOC > EEC), the Agency concludes with reasonable certainty that aggregate risks are unlikely to exceed HED's level of concen.

A summary of aggregate exposure and risk, including DWLOC calculations, may be found in Section 5.0 of this document.

4.4 Residential Exposure/Risk Pathway

4.4.1 Home Uses

4.4.1.1 Residential Handler Exposure

The Agency notes that Syngenta does not currently hold any active end-use product registrations for metolachlor. S-metolachlor is registered (as an emulsifiable concentrate formulation) for use on lawn, turf (including sod farms), golf courses, sports fields, and ornamental gardens. Although not labeled as a restricted-use pesticide, the label as it is currently marketed is not intended for homeowner purchase or use. On this basis, a residential handler is not expected to be exposed to residues of s-metolachlor. Therefore, a residential handler assessment was not conducted.

4.4.1.2 Residential Post-application Exposure

There is potential for post-application exposure to adults and children resulting from the use of s-metolachlor on residential lawns. Although the use sites for s-metolachlor vary from golf courses to ornamental gardens, the residential lawn scenario represents what the Agency considers the likely upper-end of possible exposure. Post-application exposures from various activities following lawn treatment are considered to be the most common and significant in residential settings. Post-application exposure is considered to be short-term (one to 30 days of exposure) only, based on a label specification of a six week interval before the re-application of s-metolachlor. The registrant has also indicated a label revision to limit application to one time per season.

A short-term dermal endpoint was not selected, since no systemic toxicity was seen at the limit dose of 1000 mg/kg/day; therefore, a dermal risk assessment was not conducted. Post-application inhalation exposure is also expected to be minimal since s-metolachlor is only applied in an outdoor setting, the vapor pressure is low (2.8×10^{-5} mm Hg at 25°C), and the label specifies that residents should not re-enter treated areas until after sprays have dried.

The following post-application incidental oral scenarios following application to lawns and turf have been identified: 1) short-term oral exposure to toddlers and children following hand-to-mouth exposure; 2) short-term oral exposure to toddlers and children following object-to-mouth exposure; and 3) short-term oral exposure to toddlers and children following soil ingestion. The term "incidental" is used to distinguish the inadvertent oral exposure of small children from exposure that may be expected from treated foods or residues in drinking water.

Since the FQPA safety factor for the protection of children and infants was reduced to 1X, a target MOE value of 100 has been identified for residential assessments. MOE values greater than 100 are not considered to be of concern to the Agency. MOE estimates are based on the NOAEL dose level of 50 mg/kg/day established for short-term oral risk assessment.

The HED Standard Operating Procedures for Residential Exposure Assessments (Draft, December 18, 1997) were used as a guideline for the residential post-application assessment. Also, standard values for turf transferable residues, turf transfer coefficients, and hand-to-mouth activities were used as amended by Exposure Policy 12 (Science Advisory Panel on Exposure, February 22, 2001). The exposure and risk estimates for the three residential exposure scenarios are assessed for the day of application (day "0") since children will likely contact the lawn immediately following application.

The following estimates/assumptions were used in the risk assessment:

- A single application at the maximum label rate of 2.47 lb ai/acre for s-metolachlor.
- Exposure duration for children is assumed to be 2 hours per day.
- The exposed child's weight is 15 kg (33 pounds).
- Turf transferable residue (TTR) value of 5%, and object-to-mouth residue value of 20% of the application rate assumed.

An explanation of the exposure calculations used in the assessment may be found in the Residential Risk Assessment chapter (R. Griffin memo, 2/20/2002).

The exposure estimates for the three post-application scenarios (object-to-mouth, hand-to-mouth, and incidental soil ingestion) were combined to represent the possible (if not likely) high-end oral exposure resulting from lawn (or similar) use. **Combined post-application oral risk estimates for s-metolachlor are not of concern.** Table 4 summarizes the results of the residential post-application assessment:

Table 4: Summary of Short-term Residential Post-application MOE Values

Exposure Scenario[a]	S-Metolachlor[b]	Oral Dose (mg/kg/day)	Oral Short-term MOE[c]
Object-to-mouth	S-metolachlor	0.0092	5400
Hand-to-mouth	S-metolachlor	0.037	1400
Soil ingestion	S-metolachlor	0.00012	400,000
Combined exposure	S-metolachlor	0.046	1100

[a]Exposure scenario represents oral exposure of children, with an assumed body weight of 15 kg.
[b]S-metolachlor application rate is 2.47 lb ai/acre.
[c]Short-term oral MOE = NOAEL/Dose, where short-term oral NOAEL = 50 mg/kg/day.

The Agency acknowledges that Syngenta has no remaining residential end-use product labels for racemic metolachlor; however, for informational purposes, the combined oral MOE estimate for shrt-term residential uses of metolachlor (based on EPA Reg. No. 100-691 and a label rate of 4 lb ai/acre) is 670 and **not** of concern.

4.4.2 Recreational Uses

S-metolachlor may be used on sports and recreational fields, as well as golf courses. However, the Agency believes that children's exposure to residues of s-metolachlor remaining on residential lawns after treatment represents the likely upper-end of exposure. Furthermore, since dermal and inhalation risks are not of concern, and oral exposures from sports and recreational fields, as well as golf courses, are expected to be minimal, risks for these other non-occupational settings are expected to be insignificant relative to the potential exposure from residential lawns.

4.4.3 Other (Spray Drift etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation, and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

HED has conducted a direct exposure assessment for the use of s-metolachlor on lawns, and determined that there is no risk of concern from this use. No additional risk from s-metolachlor is expected due to spray drift.

4.5 Incidents Reports

A review of metolachlor incident reports was conducted by HED in August, 1997. The following incident data bases were consulted: the OPP Incident Data System (IDS), Poison Control Centers, California Department of Pesticide Regulation; and the National Pesticide Telecommunications Network (NPTN). HED determined that no serious illnesses that could be attributed to metolachlor have been reported in data sources available to the EPA.

Although more cases of incidents involving metolachlor have been reported in Poison Control Center data and the Incident Data System since 1997, most of the cases were minor, involving skin and eye irritation. Two ingestions reported in the literature (one in a pregnant woman) did not result in significant effects. These findings do not alter the conclusions reached in the August, 1997 incident report memo (personal communication between C. Jarvis and J. Blondell on 10/29/2001).

5.0 Aggregate Risk Assessments and Risk Characterizations

5.1 Acute Risk

5.1.1 Aggregate Acute Risk Assessment

An acute aggregate risk assessment addresses potential exposure from combined residues of metolachlor/s-metolachlor on food and in drinking water (both surface and ground water). Potential residential exposures are not incorporated into an acute aggregate risk assessment. As show in Table 5a, EFED's EECs are below the Agency's DWLOC values for the parent compound, the ESA degradate, and the OA degradate. The combined value of the parent plus the degradates is also below the acute DWLOC value. The Agency concludes that acute aggregate risk estimates are not of concern for any population subgroup.

5.1.2 Acute DWLOC Calculations

Table 5a. Acute DWLOC Calculations for Metolachlor/s-Metolachlor

Population Subgroup[1]	Acute Scenario											
	aPAD mg/kg/d	Estimated Acute Food Exp mg/kg/d	Max Acute Water Exp mg/kg/day[2]	Ground Water EEC (ppb)[3]				Surface Water EEC (ppb)[3]				Acute DWLOC (µg/L)[4]
				Parent	ESA	OA	Total[5]	Parent	ESA	OA	Total	
U.S. Population	3.0	0.004111	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	104856.1
Infants <1	3.0	0.006855	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	29931.45
Children 1-2	3.0	0.008224	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	29917.76
Children 3-5	3.0	0.006965	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	29930.35
Children 6-12	3.0	0.005003	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	29949.97
Youth 13-19	3.0	0.003309	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	89900.73
Females 13-49	3.0	0.002965	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	89915.55
Adults 20-49	3.0	0.002815	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	104896.2
Adults 50+	3.0	0.002839	3.0	5.5	65.8	31.7	103	77.6	31.9	91.4	200.9	104900.6

[1] Population subgroups are representative of those with the highest dietary exposure values. Standard body weights and water consumption values are as follows: 70 kg/2L per day (adult male/general population); 60 kg/2L per day (adult female); 10 kg/1L per day (child).

[2] Maximum acute water exposure (mg/kg/day) = [(acute PAD (mg/kg/day) - acute food exposure (mg/kg/day)]

[3] The crop producing the highest level was used.

[4] Acute DWLOC(µg/L) = $\frac{\text{[maximum acute water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$; values are rounded to 2 significant figures.

[5] "Total" represents the combined value of parent plus the ESA and OA degradates and assumes the toxicity of the degradates is equivalent to metolachlor.

5.2 Short-Term Risk

5.2.1 Aggregate Short-Term Risk Assessment

A short-term aggregate risk assessment considers potential exposure from food, drinking water, and short-term, non-occuapational (residential) pathways of exposure for a duration of 1 to 30 days. For s-metolachlor, potential short-term, non-occupational risk scenarios include oral exposure of children to treated lawns. In this aggregate short-term risk assessment, exposure from food, drinking water, and residential lawns (s-metolachlor use only) has been considered. Since only children have the potential for non-occupational, short-term risk, they are the only population subgroup included below. Short-term DWLOC values have been calculated for s-metolachlor only, since Syngenta no longer holds any [racemic] metolachlor residential end-use products. As shown in Table 5b, EFED's EECs for the parent compound, the ESA degradate, and the OA degradate are below the short-term s-metolachlor DWLOC value for children. The combined value of the parent plus the degradates is also below the short-term s-metolachlor DWLOC value. The Agency concludes that short-term aggregate risks from s-metolachlor are not of concern.

For informational purposes, it is noted that the EEC values for the parent compound, ESA degradate, and the OA degradate are below the metolachlor short-term DWLOC value for children. The combined value of the parent plus the degradates is also below the metolachlor short-term DWLOC value.

5.2.2 Short-Term DWLOC Calculations

Table 5b. Short-Term Aggregate Risk and DWLOC Calculations for s-Metolachlor

Population	Short-Term Scenario														
	Target MOE[1]	MOE food[2]	MOE oral[3]	Aggregate MOE (food and residential)[6]	MOE water[7]	Allowable water exposure[8] (mg/kg/day)	Ground Water EEC[9](ppb)				Surface Water EEC[9](ppb)				DWLOC[10] (µg/L)
							Parent	ESA	OA	Total[11]	Parent	ESA	OA	Total[11]	
Children (1-2)	100	13000	1100	1000	110	0.45	5.5	65.8	32	103.3	4.3	22.8	65.1	92.2	4000

[1] The target MOE of 100 is based on the 100x uncertainty factor, and the 1x FQPA safety factor. Aggregate risks above 100 are not of concern.
[2] MOE food = [short-term oral NOAEL (50 mg/kg/day)/chronic dietary exposure of children (0.003731 mg/kg/day)]
[3] MOE oral = [short-term oral NOAEL (50 mg/kg/day)/combined hand-to-mouth, object-to-mouth, and soil ingestion oral exposure (0.046 mg/kg/day s-metolachlor)]
[4] MOE dermal = not applicable (n/a). No dermal toxicity seen at the limit dose.
[5] MOE inhalation = not applicable. Post-application inhalation exposure is expected to be minimal.
[6] Aggregate MOE (food and residential) = 1÷[[(1÷MOE food) + (1÷MOE oral)]]
[7] Water MOE = 1÷ [[(1÷ Target Aggregate MOE) - (1÷Aggregate MOE (food and residential)]]
[8] Allowable water exposure = Short-term Oral NOAEL ÷ MOE water
[9] The crop producing the highest level was used (i.e., turf)
[10] DWLOC(µg/L) = $\frac{\text{[allowable water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$; values rounded to 2 significant figures.
[11] "Total" represents the combined value of the parent plus the ESA and OA degradates and assumes the toxicity of the degradates to be equivalent to metolachlor.

5.3 Intermediate-Term Risk

5.3.1 Aggregate Intermediate-Term Risk Assessment

An intermediate-term aggregate risk assessment considers potential exposure from food, drinking water, and non-occupational (residential) pathways of exposure for a duration of 30 to 180 days. However, for metolachlor/s-metolachlor, no intermediate-term non-occupational exposure scenarios are expected to occur. Therefore, intermediate-term DWLOC values were not calculated and an intermediate-term aggregate risk assessment is not required.

5.4 Chronic Risk

5.4.1 Aggregate Chronic Risk Assessment

A chronic aggregate risk assessment considers chronic exposure from food, drinking water, and non-occupational (residential) pathways of exposure. For metolachlor and s-metolachlor, there are no chronic (greater than 180 days of exposure) non-occupational exposure scenarios. Therefore, the chronic aggregate risk assessment considers exposure from food and drinking water only. As shown in Table 5c, EFED's EECs for the parent compound, the ESA degradate, and the OA degradate are below the Agency's chronic DWLOC values for all population subgroups. The combined value of the parent plus degradates is also below the chronic DWLOC value. The Agency concludes that chronic aggregate risks are not of concern.

5.4.2 Chronic DWLOC Calculations

Table 5c. Chronic DWLOC Calculations for Metolachlor and s-Metolachlor

Population Subgroup[1]	cPAD mg/kg/day	Chronic Food Exp mg/kg/day	Max Chronic Water Exp mg/kg/day[2]	Ground Water EEC (ppb)[3]				Surface Water EEC (ppb)[3]				Chronic DWLOC[4] (µg/L)
				Parent	ESA	OA	Total	Parent	ESA	OA	Total[5]	
U.S. Population	0.1	0.001643	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	3442.50
Infants <1	0.1	0.002280	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	977.20
Children 1-2	0.1	0.004025	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	959.75
Children 3-5	0.1	0.003510	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	964.90
Children 6-12	0.1	0.002412	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	975.88
Youth 13-19	0.1	0.001515	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	2954.55
Females 13-49	0.1	0.001349	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	2962.11
Adults 20-49	0.1	0.001263	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	3452.79
Adults 50+	0.1	0.001226	0.1	5.5	65.8	31.7	103	4.3	22.8	65.1	92.2	3457.09

[1] Population subgroups are representative of those with the highest dietary exposure values. Standard body weights and water consumption values are as follows: 70 kg/2L per day (adult male/general population); 60 kg/2L per day (adult female); 10 kg/1L per day (child).
[2]Maximum Chronic Water Exposure (mg/kg/day) = [Chronic PAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]
[3]The crop producing the highest level was used.
[4] Chronic DWLOC(µg/L) = $\frac{\text{[maximum chronic water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$; values rounded to 2 significant figures.
[5] "Total" represents combined value of parent plus ESA and OA degradates and assumes the toxicity of the degradates is equivalent to metolachlor.

5.5 Cancer Risk

5.5.1 Aggregate Cancer Risk Assessment

An aggregate cancer risk assessment considers potential carcinogenic exposure from food, drinking water, and non-occupational (residential) pathways of exposure. However, as noted earlier in this risk assessment, the NOAEL that was established based on tumors in the rat (15 mg/kg/day, seen at the highest dose tested of 150 mg/kg/day) is comparable to the NOAEL of 9.7 mg/kg/day selected for establishing the chronic reference dose for metolachlor. It is assumed that the chronic dietary PAD is protective for cancer dietary risk. Therefore, a separate cancer aggregate risk assessment was not conducted, and cancer DWLOC values were not calculated.

6.0 Cumulative

The chloroacetanilide pesticides represent a class of food use pesticides that have been given high priority by OPP for the reassessment of tolerances in accordance with the mandates of FQPA. This review only covers metolachlor/s-metolachlor. The group of chloroacetanilide pesticides consists of **acetochlor**, **alachlor**, **butachlor**, **metolachlor** and **propachlor**. Various members of this group of chloroacetanilide pesticides have been shown to result in several different types of tumor responses in laboratory animals (e.g., nasal, thyroid, liver, and stomach tumors). Therefore, as part of the reassessment, OPP scientists considered several different potential common mechanism of toxicity groupings for these chemicals.

In reviewing this issue, OPP scientists were guided by several relevant Agency science policies, including *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*[1]. Additionally, on March 19, 1997, the Agency presented to the FIFRA Scientific Advisory Panel (SAP) a draft case study illustrating the application of the Common Mechanism Guidance to the grouping of chloroacetanilide pesticides based on a common mechanism of toxicity. The SAP agreed with the Agency's conclusion that there is sufficient evidence to support the grouping of certain chloroacetanilides that cause nasal turbinate tumors by a common mechanism of toxicity[2].

Upon consideration of the SAP comments, OPP's own reviews and the data underlying these reviews, as well as additional information received by the Agency from registrants or presented in the open literature since the 1997 draft document, OPP has revised its science document discussing the potential grouping of chloroacetanilide pesticides, or a subgroup of them, based on a common mechanism of toxicity.

In the revised document entitled *The Grouping of a Series of Chloroacetanilide Pesticides Based on a Common Mechanism of Toxicity*[3], OPP has concluded that only some of the pesticides that comprise the

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[1] *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity,* Office of Pesticide Programs, USEPA (issued for public comment in August, 1998; issued in revised form January 29, 1999).

[2] SAP Report, April 28, 1997. Report of the FIFRA Scientific Advisory Panel Meeting, March 19-20, 1997. Held at the Crystal Gateway Marriott, 1700 Jefferson Davis Highway, Arlington, VA 22202.

[3] *The Grouping of a Series of Chloroacetanilide Pesticides Based on a Common Mechanism of Toxicity,* Office of Pesticide Programs, USEPA (June 7, 2001).

class of chloroacetanilides should be designated as a "Common Mechanism Group" based on the development of nasal turbinate tumors by metabolism to a highly tissue-reactive moiety, i.e., quinoneimine. Thus, only acetochlor, alachlor, and butachlor should be grouped based on a common mechanism of toxicity for nasal turbinate tumors. Although metolachlor does distribute to the nasal turbinates, and might produce a quinoneimine, it is not apparent from currently available data that it shares the same target site in the nasal tissue as acetochlor, alachlor and butachlor. Although propachlor does produce a precursor of a quinoneimine, the available data do not support its tumorigenicity to the nasal turbinates.

In conclusion, it is OPP's position, at this stage in the tolerance reassessment process, that only some chloroacetanilides, namely **acetochlor, alachlor, and butachlor should be considered as a Common Mechanism Group** due to their ability to cause nasal turbinate tumors. For purposes of a cumulative risk assessment as a part of the tolerance reassessment process for acetochlor, alachlor, and butachlor, these three pesticides will be considered as a Common Mechanism Group. Following the initiation of a cumulative risk assessment, further analyses of new or existing data may occur which could impact the Agency's evaluation of specific members of this group or the group as a whole.

7.0 Data Needs/Label Requirements

Toxicology Data Needs:
The need for a 28-day inhalation study has been identified for both metolachlor and s-metolachlor. Submission of this study would allow the Agency to improve characterization regarding the concern for toxicity via the inhalation route of exposure following application of metolachlor/s-metolachlor on multiple days in a commercial setting. Registrants are recommended to follow the protocol for the 90-day inhalation study provided in OPPTS Guideline 870.3465, but cease exposure at 28 days.

Residue Chemistry Data Needs:
The following residue chemistry data deficiencies have been identified (for details on data requirements, see Revised Metolachlor and S-Metolachlor Residue Chemistry Chapter for the Tolerance Reassessment Eligibility Decision (TRED) Document. S. Kinard; 05/22/02. D282931):

- Residue data supporting the use of *S*-metolachlor (EC) on cabbage are required and the registrant should pursue a section 3 registration for s-metolachlor on cabbage.
- Residue data on corn sorghum, and soybean aspirated grain fractions are required for both metolachlor and s-metolachlor.
- A revised Section F proposing appropriate tolerances for metolachlor residues in/on grass forage and grass hay should be submitted.
- Residue data supporting shelled, succulent peas, and beans are required.
- Label amendments are required for both metolachlor and s-metolachlor use on legume vegetable foliage.
- A revised Section F proposing an appropriate tolerance for sugar beet molasses and removal of the tolerance for dried pulp should be submitted.
- Residue data supporting the use of s-metolachlor (EC) on dry bulb onions are required and the registrant should pursue a section 3 registration for s-metolachlor on onion.
- Label amendments are required for both metolachlor and s-metolachlor use on peanut.
- Additional residue data supporting bell peppers are required.
- Residue data on sorghum aspirated grain fractions are required for both metolachlor and s-

metolachlor.

- Residue data on soybean aspirated grain fractions are required for both metolachlor and s-metolachlor.
- Label amendments are required for both metolachlor and s-metolachlor use on soybean.
- Label amendments are required for metolachlor (EC) use on spinach. If the petitioner intends to support the 3.0 lb ai/A seasonal rate, then data would be required reflecting pre-emergence applications at 1.0 lb ai/A/crop to three successive spinach crops.
- The registrant must provide copies of labels including the proposed use on tomato.
- Label amendments are required for metolachlor use on tree nuts.
- Additional data are required characterizing the ^{14}C-residues in rotated crops, along with information on the percentage of the ^{14}C-residues measured by the current enforcement method, supporting storage stability data, and sample storage conditions and intervals.
- Residue data are required depicting residues in/on representative rotated cereal grains planted 4.5 months following a single application of metolachlor at the maximum rate for corn.
- Analytical grade reference standards are required as requested by the repository for metolachlor, s-metolachlor, and all metabolites of concern.

Product Chemistry Data Needs:

The following product chemistry data deficiencies have been identified:

- 830.1700 Preliminary Analysis (metolachlor; Syngenta 95% Technical)
- 830.1800 Enforcement Analytical Method (metolachlor; Syngenta 95% Technical)
- 830.7050 UV/Visible Absorption (metolachlor; Syngenta 95% Technical)

APPENDIX A

Appendix A Table 1: Toxicity Profile for Metolachlor (PC Code 108801)

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	44775401 (1999) Acceptable/guideline 0, 30, 300, 3000 ppm (M/F: 0, 2.00/2.32, 20.2/23.4, 210/259 mg/kg/day)	NOAEL for males = 3000 ppm LOAEL for males not established NOAEL for females = 300 ppm LOAEL for females = 3000 ppm based on decreased body weight/body weight gain
870.3150 180-Day oral toxicity in nonrodents	00032174 (1980), 43244001 acceptable/guideline 0, 100, 300, 1000 ppm (M/F: 0, 2.92/2.97, 9.71/8.77, 29.61/29.42)	NOAEL = 300 ppm LOAEL = 1000 ppm based on decreased body weight gain
870.3200 21/28-Day dermal toxicity	41833101 (1987) acceptable/guideline 0, 10, 100 or 1000 mg/kg/day	systemic NOAEL = 1000 mg/kg/day. systemic LOAEL was not established dermal irritation NOAEL was not established dermal irritation LOAEL = 10 mg/kg/day based on very slight erythema, dry skin and fissuring (one animal)
870.3700a Prenatal developmental in rodents	00151941 (1985) acceptable/guideline 0, 30, 100, 300 or 1000 mg/kg/day	**maternal toxicity NOAEL = 300 mg/kg/day.** **maternal toxicity LOAEL = 1000 mg/kg/day based on an increased incidence of death, clinical signs of toxicity (clonic and/or toxic convulsions, excessive salivation, urine-stained abdominal fur and/or excessive lacrimation) and decreased body weight gain.** **developmental toxicity NOAEL = 300 mg/kg/day developmental toxicity LOAEL = 1000 mg/kg/day based on slightly decreased number of implantations per dam, decreased number of live fetuses/dam, increased number of resorptions/dam and significant decrease in mean fetal body weight**
870.3700b Prenatal developmental in nonrodents	00041283 (1980) acceptable/guideline 0, 36, 120 or 360 mg/kg/day	maternal toxicity NOAEL = 120 mg/kg/day. maternal toxicity LOAEL = 360 mg/kg/day based on an increased incidence of clinical observations (persistent anorexia) and decreased body weight gain developmental toxicity NOAEL = 360 mg/kg/day developmental toxicity LOAEL was not established.
870.3800 Reproduction and fertility effects	00080897 (1981) acceptable/guideline 0, 30, 300 or 1000 ppm (F_0 males: 0, 2.4, 23.5 and 75.8 mg/kg/day; F_0 females: 0, 2.5, 26.0 and 85.7 mg/kg/day; F_1males: 0, 2.3, 23.7 and 76.6 mg/kg/day; F_1 females: 0, 2.6, 25.7 and 84.5 mg/kg/day).	Parental toxicity NOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day). Parental toxicity LOAEL was not established Reproduction toxicity NOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day). Reproduction toxicity LOAEL was not established Offspring NOAEL = 300 ppm (F_0 males/females: 23.5/ 26.0 mg/kg/day; F_1males/females: 23.7/25.7 mg/kg/day). Offspring LOAEL = 1000 ppm (F_0 males/females: 75.8/85.7 mg/kg/day; F_1males/females: 76.6/84.5 mg/kg/day) based on decreased body weight.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity dogs	40980701, 41164501, 42218601 and 42218602. (1989) acceptable/guideline 0, 100, 300 or 1000 ppm (males: 0, 3.5, 9.7 and 32.7 mg/kg/day, respectively; females: 0, 3.6, 9.7 and 33.0 mg/kg/day, respectively) for one year.	NOAEL = 300 ppm (9.7 mg/kg/day) for females LOAEL = 1000 ppm for females (33.0 mg/kg/day) based on decreased body weight gain LOAEL for males was not established; NOAEL = 1000 ppm (32.7 mg/kg/day).
870.4300 Chronic toxicity/ carcinogenicity rodents	00129377 (1983) acceptable/guideline 0, 30, 300 or 3000 ppm (0, 1.5, 15 or 150 mg/kg/day based on 1 ppm in food equals 0.05 mg/kg/day)	NOAEL = 300 ppm (15 mg/kg/day) for females LOAEL = 3000 ppm (150 mg/kg/day) for females based on slightly decreased body weight gain and food consumption. The LOAEL was not established for males. The NOAEL was 3000 ppm (150 mg/kg/day). **Administration of doses up to 3000 ppm was associated with statistically significant increases in liver adenomas and combined adenoma/carcinoma in female rats. In male rats, there was a statistically significant trend but not pair-wise significance for liver tumors.**
870.4300 Carcinogenicity mice	00117597 (1982) acceptable/guideline 0, 300, 1000 or 3000 ppm (0, 45, 150 or 450 mg/kg/day based on 1 ppm in food equals 0.150 mg/kg/day)	NOAEL = 1000 ppm (150 mg/kg/day) LOAEL = 3000 ppm (450 mg/kg/day) based on possible treatment-related deaths in females and decreased body weight/body weight gain in males and females **no evidence of carcinogenicity**
Gene Mutation 870.5100 - bacterial reverse mutation	00015397 (1976) acceptable/guideline 10, 100, 1000 and 10,000 ug/plate	negative up to cytotoxic doses (1000 ug/plate)
Gene Mutation 870.5300 - mouse lymphoma	00158929 (1984) acceptable/guideline 9.5-190 nl/ml without activation; 10.5-280 nl/ml with activation	no effect on the incidence of mutations in the presence or absence of metabolic activation
Cytogenetics 870.5395 - micronucleus assay in Chinese hamsters	00158925 (1984) acceptable/guideline 0, 1250, 2500 or 5000 mg/kg	no effect of treatment on incidence of micronuclei induction
Cytogenetics 870.5450 - dominant lethal assay in mice	00015630 (1978) acceptable/guideline 100 or 300 mg/kg	no effect on embryonic death, pre- and post-implantation or fertility rates in mated females
Other Effects 870.5550 - DNA Damage/Repair in rat hepatocytes	00142828 (1984) acceptable/guideline 0.25, 1.25, 6.25, or 31.25 nl/ml	negative

42

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Other Effects 870.5550 - DNA Damage/Repair in human fibroblasts	00142827 acceptable/guideline 0.125, 0.625, 3.125 or 15.625 nl/ml	negative
Other Effects 870.5550 - Unscheduled DNA synthesis in rat hepatocytes	43244003 (1994) acceptable/guideline 1250, 2500 or 4000 mg/kg to males; 500, 1000 or 1500 mg/kg to females	negative for induction of UDS; however, significant increases in percentage of cells in S-phase were observed in females dosed at 500 mg/kg (but not at 1000 or 1500 mg/kg) and sacrificed at 15 hours
870.7485 Metabolism and pharmacokinetics	MRID 00015425 (1974) unacceptable 52, 28 or 33 mg/kg to male rats	Conclusions: Urinary metabolites of CGA 24705 (N-(2-methoxy-1-methylethyl)-2-ethyl-6-methyl-chloroacetanilide) were identified following oral administration of 52 mg/kg, 28 mg/kg, and 33 mg/kg to male rats. Two metabolites, each comprising approximately 5% of chloroform extractable urinary radioactivity, were identified from oral administration of CGA 24705. These were the products CGA 37735 (2-ethyl-6-methyl-hydroxyacetanilide), in which N-dealkylation of R_1 (the N-(2-methoxy-1-methylethyl side chain) and side chain dechlorination and oxidation of R_2 (the N-chloroacetyl side chain) have occurred, and CGA 46129 (N-(1-carboxy-ethyl)-2-ethyl-6-methyl hydroxyacetanilide) in which the ether bond of R_1 has been split and oxidized to the corresponding carboxylic acid, while R_2 is similar to R_2 found in CGA 37735. In study #7/74, these 2 metabolites each represented approximately 5% of organic extractable urinary radioactivity, while in study #12/74, the percentage found as CGA 46129 was between 20-25% of urinary radioactivity, and CGA 37735 represented between 3-5% of organic extractable radioactivity. The major metabolic pathway proposed from analysis of urinary as well as fecal metabolites is one of cleavage of the ether bond and subsequent oxidation to the carboxylic acid, as well as hydrolytic removal of the chlorine atom. Conjugation of CGA 24705 or metabolites with gluronic acid or sulfate does not appear to occur. Aqueous extractable urinary radioactivity contained 58% of the total urinary radioactivity and was composed of 5 different radioactive fractions, which were not identified. Current guideline recommendations as to dose levels and use of both sexes in metabolism studies were not followed. Thus, whether the metabolic pattern is altered with dose or repeated exposure cannot be evaluated from these data.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	40114401 (1987) unacceptable Single low (1.5 mg/kg), single high (300 mg/kg) and repeated low (1.5 mg/kg/day for 15 days)	Conclusions: Single low (1.5 mg/kg), single high (300 mg/kg) and repeated low (1.5 mg/kg/day for 15 days) oral doses of metolachlor were readily absorbed and eliminated by male and female rats. Urinary and fecal elimination of radioactivity associated with orally administered [^{14}C] metolachlor was essentially complete within 48 to 72 hours after dosing. Low- and high-dose females eliminated ^{14}C more rapidly ($p<0.003$, half-lives of elimination, 16.6 and 15.6 hours, respectively) than low- and high-dose males and repeated-dose animals of both sexes (half-lives, 18.2 and 20.0 hours). Elimination by all animals followed first-order kinetics. Approximately one-half to two-thirds (48 to 64 percent) of the ^{14}C administered was recovered from the urine within 7 days; similar amounts were present in the feces. Low-dose males eliminated slightly more of the radioactive dose in the feces (55 percent) than the urine (48 percent). The opposite trend was seen in the low-dose females and repeated-dose rats of both sexes; these animals excreted approximately 58 to 64 percent of the ^{14}C dose in the urine and 42.5 to 46.5 percent in the feces within 7 days after dosing. High-dose animals excreted similar amounts (58 to 60 percent) of the radioactive dose in the urine and feces. Total recoveries of ^{14}C (urine, feces, and tissues) tended to be high and were between 105 and 122.5 percent. Relatively low levels of radioactivity were present in the tissues of all animals at 7 days postdosing. Tissues of low- and repeated-dose rats contained approximately 1.6 to 2.5 percent of the ^{14}C dose; tissues of high-dose rats accounted for 3.2 (females) and 4.2 (males) percent. For all groups, most of the tissue radioactivity (1.1 to 3.0 percent of the dose) was associated with red blood cells (RBCs); RBCs also contained the highest concentrations of radio labeled compound (0.6 to 0.9 ppm, low- and repeated-dose rats; 232 and 247 ppm, high-dose females and males, respectively), indicating that [^{14}C] metolachlor and/or its metabolites bind extensively to these cells. The next highest concentrations of radiolabel (0.03 to 0.13 ppm, low- and repeated-dose rats; 7.3 to 37 ppm, high-dose animals) were present in metabolically active tissues, including the heart, lung, kidney, liver and spleen. Brain, bone and muscle contained the smallest amounts of radioactivity (0.004 to 0.015 ppm, low- and repeated-dose rats; 1.7 to 3.5 ppm, high-dose rats). Tissue ^{14}C residues in high-dose males were approximately 250 to 500 times greater than those of low-dose males, indicating that the ratio of tissue concentrations (high dose:low dose) was much larger than the corresponding dose ratio of 200:1 (300 mg/kg: 1.5 mg/kg). In contrast, tissue ^{14}C levels of females were, in general, proportionate to dose. Tissues of low- and repeated-dose rats contained similar amounts of radioactivity. These data indicate that some ^{14}C was retained by all animals and that the greatest potential for accumulation of radioactivity was in male rats given a single high oral dose of [^{14}C] metolachlor.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	43164201 (1992) acceptable/guideline low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg)	In a rat metabolism study (MRID # 431642-01), ^{14}C-Metolachlor was administered orally in PEG-200 [HWI 6117-208] or corn oil [ABR-94001] to groups (5 sex/dose) of male and female Sprague-Dawley rats at a low oral dose (1.5 mg/kg), repeated low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg). Control animals (1/sex) received blank formulation. Comparison of oral and intravenous data showed that of the administered dose, between 69.6% and 93.2% was absorbed. Distribution data showed that the only significant sites of residual radioactivity at 7 days post-dose were residual carcass (0.9 - 2.2% of the administered dose) and red blood cells (0.95- 1.53 µg equivalents/gram in blood cells for all low dose male and female rats). Dosing regimen did not result in any apparent accumulation of residual radioactivity. Excretion data showed that urine and feces were both significant routes for elimination of metolachlor derived radioactivity. In the low dose groups, the urine appeared more of a predominant route for excretion in female rats than in males, whereas fecal excretion was slightly higher in males. However, at the high oral dose, there were no apparent sex-related differences in the pattern of urinary excretion. Examination of urinary excretion data as presented in graphical format indicated that at the 300 mg/kg dose, excretion was delayed vs the low oral dose, suggesting saturation of elimination. Metabolism of metolachlor in this study was complex, with up to 32 metabolites identified in urine and/or feces. The "major" urinary metabolite found in all dose groups was the metabolite designated CGA-46129. This metabolite was present as 5.6-13.1% of the total radioactive residue (TRR) in rat urine across all dose groups, and was highest in the intravenously dosed group. In the orally dosed rats, the percentage of this metabolite decreased from approximately 13% of TRR to between 5.6-9.2% of TRR. Other metabolites identified in urine which constituted near or at 5% of TRR were U10 (CGA-37735), U13, U17, U1, "polar 1", and "polar 2." The radioactivity constituting the 'polar 1' and 'polar 2' regions was further broken down to at least 12 components by TLC, but the identity of the metabolites in these regions was not demonstrated. In feces, a similarly complex metabolite profile was obtained. The "major" metabolite observed in feces, F9, was identical to U7, or CGA-46129. Except for intravenously dosed rats, where the percentage of this metabolite in feces was equivalent in male and female rats (11.6 and 13.2% of TRR, respectively), the percentage of F9 in feces of orally dosed rats was always higher in males than in females. Other fecal metabolites identified at or near 5% of TRR in feces included F2 (CGA-41638), F3 (CGA-133275), F7, F8 and F8', F16, F14, and F17. Based on these data, a scheme for metabolism of metolachlor was proposed.

Appendix A Table 2: Toxicity Profile for S-Metolachlor (PC Code 108800)

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	43928923 (1995) acceptable/guideline 0, 30, 300, 3000 or 10000 ppm (0, 1.5, 15, 150 or 500 mg/kg/day)	NOAEL = 300 ppm LOAEL = 3000 ppm based on lower body weights/body weight gains, reduced food consumption and food efficiency and increased kidney weights in males
870.3100 90-Day oral toxicity rodents	44775402 (1999) unacceptable/guideline 0, 30, 300, 3000 ppm (M/F: 0, 1.90/2.13, 20.4/23.9 and 208.0/236.0 mg/kg/day0	**NOAEL = 3000 ppm (equivalent to 208 mg/kg/day in males and 236 mg/kg/day in females** **LOAEL cannot be defined**
870.3150 90-Day oral toxicity in nonrodents	43928922 (1995) acceptable/nonguideline 0, 300, 500, 1000 or 2000 ppm (M/F: 0, 9/10, 15.1/17.2, 31.1/31.5 or 62/74 mg/kg/day)	NOAEL = 2000 ppm (M/F: 62/74 mg/kg/day) LOAEL = not established
870.3700a Prenatal developmental in rodents	43928925 (1995) acceptable/guideline 0, 5, 50, 500 or 1000 mg/kg/day	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on increased clinical signs of toxicity, decreased body weights/body weight gains, food consumption and food efficiency. **Developmental** NOAEL = 1000 mg/kg/day LOAEL = not established
870.3700b Prenatal developmental in nonrodents	43928924 (1995) acceptable/guideline 0, 20, 100 or 500 mg/kg/day	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on clinical signs of toxicity **Developmental** NOAEL = 500 mg/kg/day LOAEL = not established
Gene Mutation 870.5100 Salmonella & Escherichia/Mammalian Microsome Mutagenicity Test	43928927 (1995) acceptable/guideline 78.13-1250.0 ug/plate	In independently performed microbial mutagenicity assays, *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 and *Escherichia coli* WP2 *uvr*A were initially exposed to 312.5-5000.0 µg/plate CGA-77102 technical (95.6%) in the presence and absence of S9 activation. For the confirmatory trial, doses of 78.13-1250.0 µg/plate ±S9 were evaluated with *S. typhimurium* strains TA1535, TA1537, TA100 and TA102; concentrations of 312.5-5000.0 µg/plate ±S9 were examined with *S. typhimurium* TA 98 and *E.coli* WP2 *uvr*A. In general, doses ≥ 1250.0 µg/plate ±S9 were cytotoxic for *S. typhimurium* TA1535, TA1537, TA100 and TA102 and 5000.0 µg/plate ±S9 was slightly cytotoxic for *S. typhimurium* TA98 and *E. coli* WP2 uvrA. There was, however, no indication that CGA-77102 technical induced of a mutagenic effect in any tester strain either in the presence or the absence of S9 activation.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Cytogenetics 870.5395 Micronucleus test	43928926 (1995) acceptable/guideline 500, 1000 or 2000 mg/kg	Groups of five male and five female Tif:MAGf(SPF) mice received single oral gavage administrations of 500, 1000 or 2000 mg/kg CGA 77102 technical (95.6%). Toxic signs, similar to those seen in the preliminary range-finding studies (i.e., ataxia, tremors and/or hunched posture) were recorded for high-dose males and females throughout the 48-hour postexposure. No bone marrow cytotoxicity was seen at any dose or sacrifice time. The positive control induced the expected high yield of MPEs in males and females. There was, however, no evidence that CGA 77102 technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.
Other Effects 870.5550 Unscheduled DNA synthesis	43928928 (1995) acceptable/guideline 500, 1500, 3200 (females), 5000 (males) mg/kg	Groups consisting of three to four rats per sex received single oral gavage administrations of CGA-77102 Technical (95.6%) at doses of 500, 1500 or 5000 mg/kg (males) or 500, 1500 or 3200 mg/kg (females). Hepatocytes harvested at 15 and 38 hours were evaluated for viability and replicative DNA synthesis (RDS). For the UDS determination, additional groups (3/sex/dose) were exposed to 500 or 1500 mg/kg and the recovered hepatocytes were scored at 2 or 15 hours postexposure. Two of four females in the 3200-mg/kg group and 2 of 4 males in the 5000-mg/kg group died prior to the scheduled sacrifice at 38 hours. Severe cytotoxicity was seen in the hepatocytes recovered from 1 of 2 surviving males and both female survivors in the high-dose groups. Lower levels were neither toxic to the animals nor cytotoxic to the target cells. A clear dose-related increase in the percentage of cells in S-phase (RDS) was obtained from hepatocytes harvested 38 hours posttreatment of the male rats. The response ranged from a 5.3-fold increase at 1500 mg/kg to a 16.1-fold increase at the high dose (5000 mg/kg). In females, a marked increase in RDS was initially seen at 1500 mg/kg but the response declined over time with a 24.4-fold increase at 15 hours and a 12.2-fold increase at 38 hours. There was, however, no evidence that the CGA 77102 Technical at doses of 500 or 1500 mg/kg induced a genotoxic response at 2 or 15 hours posttreatment. We conclude, therefore, that the data indicate that CGA 77102 Technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this in vivo/in vitro rat hepatocyte RDS/UDS assay.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	44491401 (1996) acceptable/guideline single dose of 0.5 (group B1) or 100 mg/kg (group D1) radio labeled CGA-77102; 100 mg/kg/day non-radio labeled CGA 77102 for 14 days followed by 0.5 mg/kg radio labeled CGA-77102 (Group V1); single dose of 0.5 or 100 mg/kg radio labeled CGA-77102 for bile-cannulation study	In all three dose groups (B1, D1, and V1), the seven day combined levels of radioactivity in urine were 31.1 - 36.5% for males and 40.8 - 45.5% for females; the fecal levels were 60.2 - 62.5% for males and 48.9 - 55.0% for females. Only 0.1% or less was eliminated in the expired air. The total recovery ranged from 96.5 ± 2.3% to 99.3 ± 0.9%. The route or extent of excretion was slightly influenced by the sex of the animal but not by pretreatment with non-radio labeled CGA-77102 or by the dose level. The degree of absorption, based on adding the cumulative urinary excretion to the total residues in tissues, was 35 - 39% in males and 43 - 49% in females of both dose groups. However, based on the bile duct cannulation study, most of CGA-77102 was absorbed from the gastrointestinal tract since 85% of the dose was recovered in urine, bile fluid, and tissues during the 48 hours study period. Therefore, the biliary excretion and enterohepatic circulation play a significant role in the elimination process of CGA-77102. Irrespective of the dose and sex, there seems to be a biphasic plasma profile with two concentration maxima (C_{max}); a fast rising first C_{max} was reached at 0.25 - 1 hour post dosing which was succeeded by a second C_{max} at 8 and at 12 - 24 hours following administration of the low and high dose, respectively. In the low dose group (B1), the first and second C_{max} were nearly identical (~ 0.03 µg/ml); in the high dose group (D1), the first and second C_{max} were, respectively, 4.6 and >3.9 µg/ml in males and 2.2 and 4.5 µg/ml in females. The time to half maximum plasma concentration ($t_{cmax/2}$) in males/females was 31/24 hours at the low dose and 44/32 hours at the high dose. Bioavailability, or the area under the plasma concentration curve (AUC_{0-48hr}), was nearly identical (~ 0.8 mg/kg.hr) among males and females of the low dose group. Also, both sexes in the high dose group had similar plasma AUC_{0-48hr} (M/F: 143/125 mg/kg.hr) which increased almost proportionately with the 200-fold increase in the dose level. The residues in RBC increased steadily with time reaching peak levels (at 24 - 48 hours post-dosing) of 0.5-0.6 and 90 ppm (or µg/g) CGA-77102 equivalents for the low (B1) and high (D1) dose groups, respectively. The peak levels in RBC remained high and were nearly 20 fold higher than the respective plasma C_{max} levels.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		The kinetics of tissue distribution and depletion in both sexes were also followed for up to 144 hours following a single low or high oral dose (Groups F1 - F4). Peak residue levels were reached within 12 - 24 hours and ranged from 0.007 ppm (female muscle) to 0.123 ppm (male kidneys) at the low dose, and from 1.29 ppm (male brain) to 16.82 ppm (male liver) at the high dose, with the highest levels being among some of the well-perfused tissues (e.g., liver, kidneys, spleen, and lungs). The extent of residue depletion was variable among the tissue types but was minimally affected by the dose or the sex of the animal. The radiolabel was most persistent in some of the well-perfused organs (e.g., the heart, lungs, and spleen) in addition to the brain and bone where, after 144 hours, the levels were decreased to only 45 - 94% of their maximal concentrations. In Groups F1 - F4, peak residue concentration in the whole blood (0.2 and 42 - 47 µg/ml in the low and high dose groups, respectively) was reached at 24 hours and was maintained throughout the study. Overall, the high/low dose peak tissue levels (including blood) ranged from 132 to 282 which approximates the 200-fold increase in dosage. CGA-77102 has a high affinity for and a long half-life in blood (especially RBC) which might contribute to the retarded depletion of tissue residues.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	44491402 (1996) unacceptable/guideline single dose of 0.5 (group B1) or 100 mg/kg (group D1) radio labeled CGA-77102; 100 mg/kg/day non-radio labeled CGA 77102 for 14 days followed by 0.5 mg/kg radio labeled CGA-77102 (Group V1); single dose of 0.5 or 100 mg/kg radio labeled CGA-77102 for bile-cannulation study (from MRID 44491401) single oral low dose (0.5 mg/kg, Group B2) of [Phenyl-U-^{14}C] CGA-24705 (R/S-Metolachlor, racemate)	The 72 hour mean recovery of radioactivity in urine, feces, and carcass following administration of 0.5 mg/kg of [Phenyl-U-^{14}C] CGA-24705 was 43.1%, 47.0%, and 7.4% in males and 54.0%, 39.4%, and 4.1% in females, respectively. In contrast, both sexes excreted more of the label in the feces (M:F 59.7%:53.4%) than in the urine (M:F 29.4%:39.8%) during the same period following administration of the same dose of [Phenyl-U-^{14}C] CGA-77102 (the S-enantiomer) (MRID 44491401). The urinary and fecal metabolite profiles, with 31 and 15 metabolite fractions, respectively, were qualitatively similar among all groups; however, there were large quantitative differences, based on the dosing formulation, on one hand, and the sex of the animal, on the other. Based on a percentage of the dose, several of the major urinary metabolite fractions (e.g., U1, U2, U3, U18, U24, and U30) were more abundant in the case of the racemic-Metolachlor (CGA-24705) than the S-Metolachlor (CGA-77102); in contrast, several fecal metabolite fractions (e.g., F9, F10, F12, and F13) were present at higher levels in the case of CGA-77102 than CGA-24705. On the other hand, there were sex-related differences regardless of the dosing formulation where, for instance, females had greater urinary concentrations than males of several metabolite fractions, including U3, U4, U8, U9, U18, U20, and U30; the males, however, excreted more of fractions U1 and U24 than the females. Also, several fecal fractions including F1, F3, F5, F6, F7, F8, and F13 were influenced by the sex regardless of the dose level (e.g. B1 vs. D1) or the stereochemical make-up of Metolachlor (B1 vs. B2). Other metabolite fractions were dependent on both the sex and the chemical formulation as, for instance, in the case of metabolite U2 which, relative to the opposite sex within the same group, was more abundant in the urine of the females of Group B2 (CGA-24705) and in the urine of the males of Group B1 (CGA-77102). The bile fluid accounted for 79.8% of the administered low or high dose of CGA-77102 (Groups G1 and G2) where the 2D-TLC showed 14 biliary metabolite fractions (G1-G14) in the high dose Group and only six metabolites in the low dose Group. The two metabolite fractions G7 and G8 accounted, respectively, for 33.3% and 9.6% of the administered low dose and 31.3% and 14.6% of the administered high dose. Other major biliary metabolites were G3, G9, and G10 which accounted for about 5%, 5-7%, and 3-5%, respectively, of either dose group.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
		The results clearly show that the metabolite profile in excreta and bile fluid is very complex and that Metolachlor (racemate or S-enantiomer) is extensively metabolized. This was also shown earlier by another rat metabolism study on the absorption, distribution, excretion, and metabolite identification of racemic CGA-24705 (MRID 43164201, reviewed by T. McMahon, HED doc. no. 010990 dated May 23, 1994). No actual metabolites or pathways were identified in the current study and there were no data to support or refute the previous findings of four major degradation pathways with more than 30 metabolites. However, knowing the enantiomeric stereospecific reactions/metabolites is not likely to help in making comparative risk assessments between R/S-Metolachlor (CGA-24705) and S-Metolachlor (CGA-77102) since the contribution of each metabolite to the overall toxicity of Metolachlor is not well understood. Furthermore, other bridging animal studies with CGA-77102 should highlight possible toxicity differences from the well-studied CGA-24705 due to variations in the metabolite profiles. The Registrant is requested to comment on or provide information on a number of issues including: 1) The stereoisomeric purity of CGA-24705 and CGA-77102. 2) The adequacy of the storage conditions and the validity of the metabolite profile results in light of the storage-related results variability. 3) Explain why, relative to the other dosing formulation, some metabolite fractions (e.g., F10, F12, and F13) were up to 7-fold higher in the case of the S-enantiomer (CGA-77102) while some urinary metabolite fractions (e.g., U1, U2, and U3) were up to 4-fold higher in the case of CGA-24705. 4) Provide rational for dose selection. 5) The Registrant might also have to comment on the possible formation and the level of methylethylaniline from either dosing formulation and the possible contribution of this metabolite to the carcinogenicity of Metolachlor. This issue was raised earlier by T. McMahon (HED document no. 010990 dated May 23, 1994) and might need to be followed up by HED's risk assessors who are in charge of S-Metolachlor.

Appendix A Table 3: Tolerance Reassessment Summary for Metolachlor (PC Code 108801)

Commodity	Current Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances listed under 40 CFR §180.368(a):				
Almond, hulls	0.3	Data were not available for review (DNA)	TBD	
Barley, fodder	0.5	Not applicable (NA)	Reassign to 180.368(d) To be determined (TBD)	Additional data are required. The definition for fodder should be changed to *Barley, straw*
Barley, grain	0.1			
Buckwheat, grain	0.1			
Cabbage	1.0	NA	Revoke	Registered uses (SLNs) on cabbage have been canceled.
Cattle, fat	0.02	Extrapolating to a 1x feeding level, maximum combined residues would be <0.011 ppm in fat, <0.016 ppm in meat, 0.035 ppm in liver, and 0.11 ppm in kidney.	0.04	Tolerances for fat, meat, and meat byproducts (except kidney) should be set at the method LOQ of 0.04 ppm. The tolerance for liver should be revoked, and the tolerance for kidney should remain at 0.2 ppm.
Cattle, kidney	0.2		0.20	
Cattle, liver	0.05		Revoke	
Cattle, meat	0.02		0.04	
Cattle, meat byproducts (exc. liver and kidney)	0.02		0.04	
Celery	0.1	NA	Revoke	Registered uses (SLNs) on celery have been canceled.
Corn, fodder	8.0	field (0.11-2.81) sweet (0.24-5.54)	6.0	*Corn, Stover.* The available metolachlor residue data indicate that the tolerance can be lowered to 6.0 ppm
Corn, forage	8.0	field (<0.12-3.02) sweet (0.27-5.75)	6.0	The available metolachlor residue data indicate that the tolerance can be lowered to 6.0 ppm
Corn, fresh (inc. sweet) (K+CWHR)	0.1	<0.08-<0.10	0.10	*Corn, sweet (K+CWHR)*
Corn, grain	0.1	<0.08	0.10	
Cotton, undelinted seed	0.1	<0.08	0.10	
Egg	0.02	Residues were not detected in eggs of hens dosed at up to 5.7x the MTDB	0.04	The tolerance for eggs should be set at the combined LOQ for the enforcement method.
Goat, fat	0.02	See cattle above	0.04	See cattle above.
Goat, kidney	0.2		0.20	
Goat, liver	0.05		Revoke	
Goat, meat	0.02		0.04	
Goat, meat byproducts (exc. liver and kidney)	0.02		0.04	

Commodity	Current Tolerance (ppm) *	Range of residues (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Hog, fat	0.02	NA	Revoke	Based on the results of the ruminant feeding study and a MTDB for swine of 0.315 ppm, there is no reasonable expectation of finding quantifiable residues in hog tissues [40 CFR 180.6(a)(3)].
Hog, kidney	0.2			
Hog, liver	0.05			
Hog, meat	0.02			
Hog, meat byproducts (exc. liver and kidney)	0.02			
Horse, fat	0.02	See cattle above	0.04	See cattle above.
Horse, kidney	0.2		0.20	
Horse, liver	0.05		Revoke	
Horse, meat	0.02		0.04	
Horse, meat byproducts (exc. liver and kidney)	0.02		0.04	
Legume vegetables group foliage (exc. soybean forage and hay)	15.0	forage (0.44-11.5) hay (0.31-2.2)	15	Residue data for forage (vines) reflect a ~60-day PHI and residue data on hay reflect at 120 day PHI.
Milk	0.02	Extrapolating to a 1x feeding level, maximum combined residues in milk would be 0.004 ppm	0.02	
Millet, fodder	0.5	NA	Reassign to 180.368(d) TBD	Additional data are required. The definition for fodder should be changed to *millet, straw.*
Millet, forage	0.5			
Millet, grain	0.1			
Milo, fodder	0.5	NA	Revoke	Residues on milo commodities are covered by tolerances on sorghum.
Milo, forage	0.5			
Milo, grain	0.1			
Nongrass animal feed (forage, fodder, straw, hay) group	3.0	forage - <0.08-0.54 hay - <0.08-<0.47	1.0 Reassign to 180.368(d)	The available alfalfa and clover data indicate that the tolerance can be reduced to 1.0 ppm.
Oats, fodder	0.5	NA	Reassign to 180.368(d) TBD	Additional data are required. The definition for fodder should be changed to *oats, straw.*
Oats, forage	0.5			
Oats, grain	0.1			
Peanut	0.5	<0.08-0.19	0.20	*Peanut, nutmeats.* New residue data indicate that the tolerance can be lowered to 0.2 ppm.
Peanut, forage	30.0	NA	Revoke	Peanut forage is no longer listed a regulated commodity of peanuts
Peanut, hay	30.0	1.04-16.5	20.0	New residue data indicate that the tolerance can be lowered to 20.0 ppm.
Peppers, bell	0.1	<0.02-0.108	Revoke	Registered uses (SLNs) on peppers have been canceled.

Commodity	Current Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Potato	0.2	<0.08-0.14	0.20	
Poultry, fat	0.02	Residues were not detected in tissues of hens dosed at up to 5.7x the MTDB	0.04	Tolerances for poultry tissues should be set at the combined LOQ for the enforcement method, and the separate tolerance for liver should be revoked.
Poultry, liver	0.05		Revoke	
Poultry, meat	0.02		0.04	
Poultry, meat byproducts (exc. liver)	0.02		0.04	
Rice, fodder	0.5	NA	Reassign to 180.368(d) TBD	Additional data are required. The tolerance for rice forage should be revoked as it is not a regulated commodity, and the definition for fodder should be changed to *rice, straw.*
Rice, forage	0.5		Revoke	
Rice, grain	0.1		Reassign to 180.368(d) TBD	
Rye, fodder	0.5	NA	Reassign to 180.368(d) TBD	Additional data are required. The tolerance for rye fodder should be changed to *rye, straw.*
Rye, forage	0.5			
Rye, grain	0.1			
Safflower, seed	0.1	<0.08	0.10	
Seed and pod vegetables (exc.soybean)	0.3	<0.08-0.44	0.50	*Edible-podded legume vegetables subgroup.* The available data support a tolerance of 0.5 ppm on this subgroup.
		<0.08-<0.11	0.10	*Dried shelled pea and bean (except soybean) subgroup* The available data support a tolerance of 0.1 ppm on this subgroup.
		NA	TBD	*Succulent shelled pea and bean subgroup* Data are required for this subgroup.
Sheep, fat	0.02	see cattle above	0.04	See cattle above
Sheep, kidney	0.2		0.20	
Sheep, liver	0.05		revoke	
Sheep, meat	0.02		0.04	
Sheep, meat byproduct (exc. liver and kidney)	0.02		0.04	
Sorghum grain, fodder	2.0	<0.11-3.19	4.0	*Sorghum grain, stover* The available data support increasing the tolerance on stover to 4.0 ppm and decreasing the tolerance on forage to 1.0 ppm
Sorghum grain, forage	2.0	<0.08-0.45	1.0	
Sorghum grain, grain	0.3	0.08-0.19	0.30	
Soybean	0.2	<0.08-<0.18	0.20	*Soybean, seed*

Commodity	Current Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Soybean, forage	8.0	0.15-4.37	5.0	The available data indicate that the tolerance on forage can be lowered to 5.0 ppm
Soybean, hay	8.0	0.38-6.90	8.0	
Fruit, stone, group	0.1	<0.08-0.08	Revoke	The registrant no longer wishes to support the use on stone fruits.
Nuts, tree, group	0.1	<0.08-0.08	0.10	
Wheat, fodder	0.5	NA	Reassign to 180.368(d) TBD	Additional data are required. The definition for fodder should be changed to *wheat, straw.*
Wheat, forage	0.5			
Wheat, grain	0.1			
Time-limited Tolerances Listed under 40 CFR §180.368(b):				
Grass, forage	10.0 [b]	0.04-8.4	10	Permanent tolerances are pending.
Grass, hay	0.2 [b]	<0.08-0.11	0.20	
Spinach	0.3 [b]	<0.08-0.38	0.50	New data support an increased permanent tolerance for metolachlor residues of 0.5 ppm in/on spinach (PP# 8E5011).
Tomato	0.1 [c]	<0.08-0.08	0.10	New data support a permanent tolerance for metolachlor residues of 0.1 ppm in/on tomato (PP#6F4751).
Tomato, puree	0.3 [c]	<0.10	Revoke	New data indicate that the tolerances for metolachlor residues in/on tomato paste and puree are not necessary.
Tomato, paste	0.6 [c]	<0.10	Revoke	
Tolerances with Regional Registrations Listed under 40 CFR §180.368(c):				
Onion, dry bulb	1.0	<0.08-<0.43 ppm	Revoke	Registered uses (SLNs) of metolachlor on onions and various peppers have been canceled.
Pepper, chili	0.5	<0.02-0.03	Revoke	
Pepper, tabasco	0.5	0.09-0.45	Revoke	
Pepper, cubanelle	0.1	0.03-0.04	Revoke	
Tolerances Needed under 40 CFR §180.368(a)(1):				
Cotton, gin byproducts	None	0.08-3.2	4.0	New residue data indicates that a tolerance of 4.0 ppm may be established.
Peanut, meal	None	<3.85	0.40	The available processing data indicates that residues concentrate in presscake (1.75x).

[a] Expressed in terms of metolachlor
[b] Time limited tolerances on grass forage and hay and spinach were set to expire on 12/31/01.
[c] Time limited tolerances on tomato commodities are set to expire on 6/30/02.
[d] Based on current residue data for peanuts, additional data are required to support the current lower use rate.

Appendix A Table 4: Tolerance Reassessment Summary for s-Metolachlor (PC Code 108800)

Commodity	Current/ Proposed Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Assessment/ Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances needed under 40 CFR §180.368(a)(2):				
Cabbage	1.0	NA	TBD	Additional data are required to support the use of *S*-metolachlor on cabbage and the registrant should pursue a section 3 registration.
Cattle, fat	0.02	Extrapolating to a 1x feeding level, maximum combined residues would be <0.011 ppm in fat, <0.016 ppm in meat, 0.035 ppm in liver, and 0.11 ppm in kidney.	0.04	Tolerances for fat, meat, and meat byproducts (except kidney) should be set at the method LOQ of 0.04 ppm, but the tolerance for kidney should remain at 0.2 ppm.
Cattle, kidney	0.2		0.20	
Cattle, meat	0.02		0.04	
Cattle, meat byproducts (exc. kidney)	0.02		0.04	
Celery	0.1	<0.08	0.10	The available metolachlor data support a tolerance of 0.10 ppm for s-metolachlor.
Corn, fodder	8.0	field (0.11-2.81) sweet (0.24-5.54)	6.0	*Corn, Stover.* The available metolachlor residue data indicate that the tolerance can be lowered to 6.0 ppm
Corn, forage	8.0	field (<0.12-3.02) sweet (0.27-5.75)	6.0	The available metolachlor residue data indicate that the tolerance can be lowered to 6.0 ppm
Corn, fresh (inc. sweet) (K+CWHR)	0.1	<0.08-<0.10	0.10	*Corn, sweet (K+CWHR)* Supported by the available metolachlor data.
Corn, grain	0.1	<0.08	0.10	*Corn, Field, grain.* Supported by the available metolachlor data.
Cotton, undelinted seed	0.1	<0.08	0.10	Supported by the available metolachlor data.
Cotton, gin byproducts	NA	0.08-3.2	4.0	New metolachlor residue data indicates that a tolerance of 4.0 ppm may be established.
Egg	0.02	Residues were not detected in eggs of hens dosed at up to 5.7x the MTDB	0.04	The tolerance for eggs should be set at the combined LOQ for the enforcement method.
Goat, fat	0.02	See cattle above	0.04	See cattle above
Goat, kidney	0.2		0.20	
Goat, meat	0.02		0.04	
Goat, meat byproducts (exc. kidney)	0.02		0.04	
Horse, fat	0.02	See cattle above	0.04	See cattle above.

Commodity	Current/ Proposed Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Assessment/ Reassessment (ppm)	Comment/*Correct Commodity Definition*
Horse, kidney	0.2		0.20	
Horse, meat	0.02		0.04	
Horse, meat byproducts (exc. kidney)	0.02		0.04	
Legume vegetables group foliage (exc. soybean forage and hay)	15.0	forage (0.44-11.5) hay (0.31-2.2)	15	Residue data for forage (vines) reflect a ~60-day PHI and residue data on hay reflect at 120 day PHI.
Milk	0.02	Extrapolating to a 1x feeding level, maximum combined residues in milk would be 0.004 ppm	0.02	
Peanut	0.5	<0.09	0.20	*Peanut, nutmeats.* New metolachlor residue data indicate that the tolerance can be lowered to 0.2 ppm.
Peanut, hay	30.0	-4.19	20.0	New metolachlor residue data indicate that the tolerance can be lowered to 20.0 ppm.
Peppers, bell	0.1	<0.02-0.108	TBD	Additional data are required for a general tolerance on peppers.
Potato	0.2	<0.08-0.14	0.20	Supported by the available metolachlor data.
Poultry, fat	0.02	Residues were not detected in tissues of hens dosed at up to 5.7x the MTDB	0.04	Tolerances for poultry tissues should be set at the combined LOQ for the enforcement method, and the separate tolerance for liver should be revoked.
Poultry, meat	0.02		0.04	
Poultry, meat byproducts (exc. liver)	0.02		0.04	
Safflower, seed	0.1	<0.08	0.10	Supported by the available metolachlor data.
Seed and pod vegetables (exc.soybean)	0.3	<0.08-0.44	0.50	*Edible-podded legume vegetables subgroup.* The available data support a tolerance of 0.5 ppm on this subgroup.
		<0.08-<0.11	0.10	*Dried shelled pea and bean (except soybean) subgroup* The available data support a tolerance of 0.1 ppm on this subgroup.
		NA	TBD	*Succulent shelled pea and bean subgroup* Data are required for this subgroup.
Sheep, fat	0.02	see cattle above	0.04	See cattle above
Sheep, kidney	0.2		0.20	
Sheep, meat	0.02		0.04	

Commodity	Current/ Proposed Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Assessment/ Reassessment (ppm)	Comment/*Correct Commodity Definition*
Sheep, meat byproducts (exc. kidney)	0.02		0.04	
Sorghum grain, fodder	2.0	<0.11-3.19	4.0	*Sorghun, stover.* The available data support increasing the tolerance on stover to 4.0 ppm and decreasing the tolerance on forage to 1.0 ppm
Sorghum grain, forage	2.0	<0.08-0.45	1.0	
Sorghum grain, grain	0.3	0.08-0.19	0.30	
Soybean	0.2	<0.08-<0.18	0.20	*Soybean, seed.* Supported by the available metolachlor and s-metolachlor data.
Soybean, forage	8.0	0.15-4.37	5.0	The available metolachlor data indicate that the tolerance on forage can be lowered to 5.0 ppm.
Soybean, hay	8.0	0.38-6.90	8.0	
Soybean, hulls	None	<0.14	None	New s-metolachlor data indicate that s-metolachlor residues in/on soybean hulls will not exceed the established tolerance on soybean seeds.
Time-limited Tolerances needed under 40 CFR §180.368(b)(2):				
Grass, forage	10.0 [b]	0.04-8.4	10	Permanent tolerances are pending.
Grass, hay	0.2 [b]	<0.08-0.11	0.20	
Spinach	0.3 [b]	<0.08-0.38	0.50	New metolachlor data support an increased permanent tolerance for s-metolachlor residues of 0.5 ppm in/on spinach.
Tomato	0.1 [c]	<0.08-0.08	0.10	New metolachlor data support a permanent tolerance for s-metolachlor residues of 0.1 ppm in/on tomato.
Tomato, puree	0.3 [c]	<0.10	revoke	New metolachlor residue data indicate that the tolerances for s-metolachlor residues in/on tomato paste and puree are not necessary.
Tomato, paste	0.6 [c]	<0.10	revoke	
Tolerances with Regional Registrations needed under 40 CFR §180.368(c)(2):				
Onion, dry bulb	1.0	<0.08-<0.43 ppm	0.50	The available metolachlor residue data support lowering the tolerance to 0.5 ppm; however, additional data are required to support the use of s-metolachlor and the registrant should pursue a section 3 registration.
Pepper, chili	0.5	<0.02-0.03	0.10	With the exception of chili peppers, the available residue data support the current tolerances. Tolerances for chili peppers could be lowered to 0.1 ppm. If a general tolerance on peppers is established at 0.5 ppm, than these separate tolerances should be revoked.
Pepper, tabasco	0.5	0.09-0.45	0.50	
Pepper, cubanelle	0.1	0.03-0.04	0.10	
Tolerances Needed under 40 CFR §180.368(d)(2):				
Barley, grain	0.5	NA	TBD	Additional data are required.
Barley, hay	None			

Commodity	Current/ Proposed Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Assessment/ Reassessment (ppm)	Comment/*Correct Commodity Definition*
Barley, straw	0.1			
Buckwheat, grain	0.1	NA	TBD	Additional data are required
Millet, forage	0.5	NA	TBD	Additional data are required.
Millet, grain	0.1			
Millet, hay	None			
Millet, straw	0.5			
Nongrass animal feed (forage, fodder, straw, hay) group	3.0	forage - <0.08-0.54 hay - <0.08-<0.47	1.0	The available alfalfa and clover data indicate that the tolerance can be reduced to 1.0 ppm.
Oats, forage	0.5	NA	TBD	Additional data are required.
Oats, grain	0.1			
Oats, hay	None			
Oats, straw	0.5			
Peanut, meal	None	<3.85	0.40	The available metolachlor processing data indicates that residues concentrate in presscake (1.75x).
Rice, grain	0.1	NA	TBD	Additional data are required.
Rice, straw	0.5			
Rye, forage	0.5	NA	TBD	Additional data are required.
Rye, grain	0.1			
Rye, straw	0.5			
Wheat, forage	0.5	NA	TBD	Additional data are required.
Wheat, grain	0.1			
Wheat, hay	None			
Wheat, straw	0.5			
Proposed Tolerances under 40 CFR §180.368(b)(2):				
Asparagus	0.10	NA	TBD	Pending review of available residue data.
Carrot	0.10	NA	TBD	Pending review of available residue data.
Horseradish	0.20	NA	TBD	Pending review of available residue data.
Peppers	0.50	NA	TBD	Pending review of available residue data.
Rhubarb	0.10	NA	TBD	Pending review of available residue data.

Commodity	Current/ Proposed Tolerance (ppm) [a]	Range of residues (ppm)	Tolerance Assessment/ Reassessment (ppm)	Comment/*Correct Commodity Definition*
Sugar beet, dried pulp	1.0	<0.50	NA	A tolerance in sugar beet dried pulp will not be required because the concentration factor was only 1.1x, and the maximum expected residues in dried pulp (0.36 ppm) will not exceed the proposed tolerance for sugar beet roots (0.5 ppm).
Sugar beet, molasses	3.0	<2.0	2.0	Based on the HAFT of 0.33 ppm for sugar beet roots, the available residue data support a tolerance of 2.0 ppm in molasses for the combined residues of S-metolachlor (CGA-37913 plus CGA-49751). The proposed tolerance of 3.0 ppm for molasses is too high.
Sugar beet, root	0.50	<0.08-0.33	0.50	The available residue data support the proposed tolerance.
Sugar beet, top	15.0	<0.08-14.5	15.0	The available residue data support the proposed tolerance.
Sunflower, seed	0.50	<0.08-<0.49	0.50	The available residue data support the proposed tolerance.
Sunflower, meal	1.0	<0.38-<0.71	1.0	Based on the HAFT of 0.47 ppm for sunflower seed and the 1.8x processing factor for meal, the maximum expected residues in sunflower meal would be 0.85 ppm. These data would support the proposed tolerance of 1.0 ppm in sunflower seed meal.
Swiss chard	0.10	NA	TBD	Pending review of available residue data.

[a] Expressed in terms of s-metolachlor
[b] Time limited tolerances on grass forage and hay and spinach were set to expire on 12/31/01.
[c] Time limited tolerances on tomato commodities are set to expire on 6/30/02.